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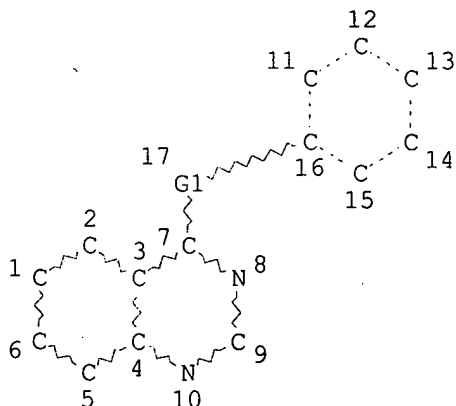
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FILE COVERS 1907 - 8 May 2003 VOL 138 ISS 19  
 FILE LAST UPDATED: 7 May 2003 (20030507/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

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 L1 STR



VAR G1=N/S/O/C  
 NODE ATTRIBUTES:  
 DEFAULT MLEVEL IS ATOM  
 DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:  
 RING(S) ARE ISOLATED OR EMBEDDED  
 NUMBER OF NODES IS 17

STEREO ATTRIBUTES: NONE  
 L3 11589 SEA FILE=REGISTRY SSS FUL L1  
 L4 16 SEA FILE=REGISTRY ABB=ON PLU=ON C-JUN?/CN  
 L6 918 SEA FILE=HCAPLUS ABB=ON PLU=ON L3  
 L7 9764 SEA FILE=HCAPLUS ABB=ON PLU=ON L4 OR CJUN OR C(W)JUN  
 L9 9 SEA FILE=HCAPLUS ABB=ON PLU=ON L6 AND L7

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L9 ANSWER 1 OF 9 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:845560 HCAPLUS

DOCUMENT NUMBER: 137:353051

TITLE: Preparation of quinazolines as TGF- $\beta$ . and/or p38- $\alpha$ . kinase inhibitors

INVENTOR(S): Chakravarty, Sarvajit; Dugar, Sundeeep; Perumattam, John J.; Schreiner, George F.; Liu, David Y.; Lewicki, John A.

PATENT ASSIGNEE(S): Scios, Inc., USA

SOURCE: U.S., 37 pp., Cont.-in-part of U.S. 6,184,226.

CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

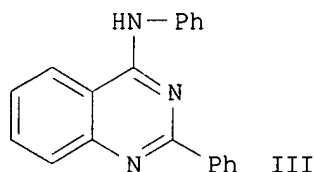
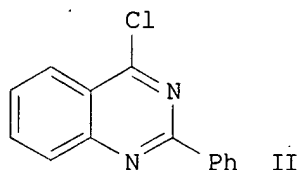
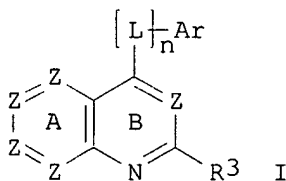
FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6476031	B1	20021105	US 1999-383825	19990827
US 6184226	B1	20010206	US 1998-141916	19980828
US 6277989	B1	20010821	US 2000-525034	20000314
US 2003069248	A1	20030410	US 2001-969936	20011002
US 2002161010	A1	20021031	US 2001-972582	20011005
PRIORITY APPLN. INFO.:			US 1998-141916	A2 19980828
			US 1999-383825	A3 19990827

OTHER SOURCE(S): MARPAT 137:353051

GI



AB Title compds. I [R3 = (un)substituted arom.; Ar = (un)substituted monocyclic or polycyclic arom.; L = S(CR22)m, NR1SO2(CR22)1, SO2(CR22)m, etc.; Z = CR2, N with the provisos that no more than two Z positions in ring A are N and wherein two adjacent Z positions in ring A cannot be N; R2 = H, alkyl, alkenyl, etc.; l = 0-3; m = 0-4; n = 1] and their pharmaceutically acceptable salts were prepd. For example, condensation of chloroquinazoline II and 4-aminopyridine afforded claimed quinazoline III. In p38- $\alpha$ . kinase inhibition studies, 9-examples of compds. I exhibited IC50 values in the range of 0.1-1.5  $\mu$ M. Also, the specificity of compds. I for p38- $\alpha$ . was assessed by their ability to

inhibit other kinases, e.g., p38-y JNK1, PKA, PKC, PK(PKD), cck2 and EGF-R, with IC50 values ranging from 4.2 - >500 .mu.M. Compds. I are useful anti-inflammatory agents and in the treatment of fibroproliferative diseases.

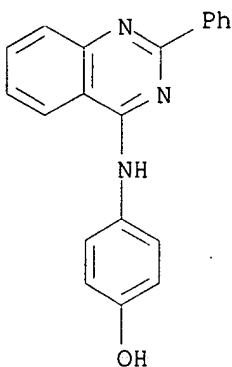
IT 54665-94-0P 157862-99-2P 259870-36-5P  
 420831-73-8P 422561-07-7P 438247-46-2P  
 446829-19-2P 474289-40-2P 474289-54-8P  
 474289-68-4P 474289-70-8P 474289-79-7P  
 474289-93-5P 474289-95-7P 474290-15-8P  
 474290-23-8P 474290-26-1P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(drug candidate; prepn. of quinazolines as TGF-.beta. and/or p38-.alpha. kinase inhibitors)

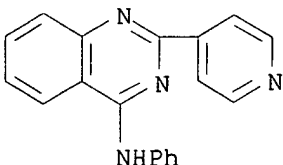
RN 54665-94-0 HCAPLUS

CN Phenol, 4-[(2-phenyl-4-quinazolinyl)amino]- (9CI) (CA INDEX NAME)



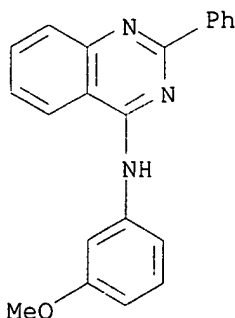
RN 157862-99-2 HCAPLUS

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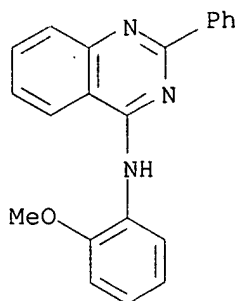


RN 259870-36-5 HCAPLUS

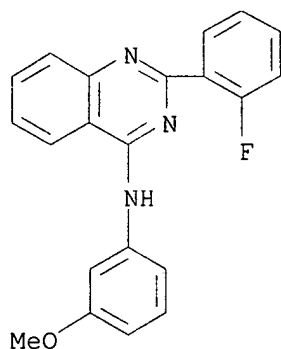
CN 4-Quinazolinamine, N-(3-methoxyphenyl)-2-phenyl- (9CI) (CA INDEX NAME)



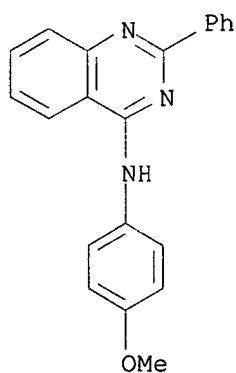
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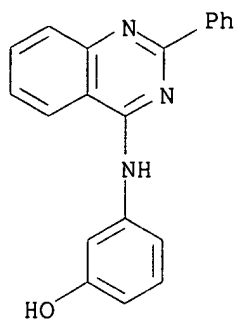
RN 422561-07-7 HCAPLUS  
 CN 4-Quinazolinamine, 2-(2-fluorophenyl)-N-(3-methoxyphenyl)- (9CI) (CA INDEX NAME)



RN 438247-46-2 HCAPLUS  
 CN 4-Quinazolinamine, N-(4-methoxyphenyl)-2-phenyl- (9CI) (CA INDEX NAME)

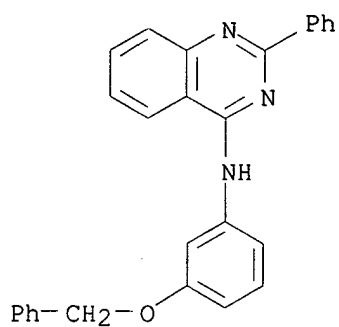


RN 446829-19-2 HCAPLUS  
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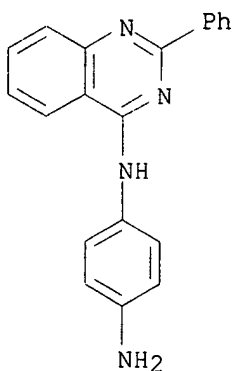
RN 474289-40-2 HCAPLUS

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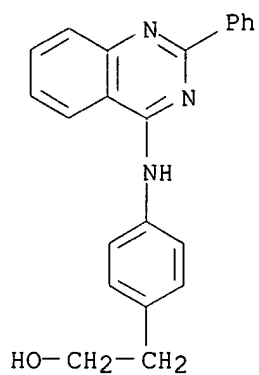
RN 474289-54-8 HCAPLUS

CN 1,4-Benzenediamine, N-(2-phenyl-4-quinazolinyl)- (9CI) (CA INDEX NAME)



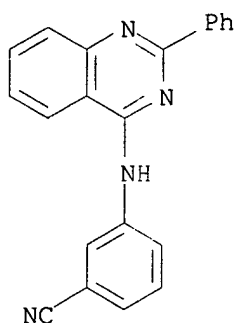
RN 474289-68-4 HCAPLUS

CN Benzeneethanol, 4-[(2-phenyl-4-quinazolinyl)amino]- (9CI) (CA INDEX NAME)



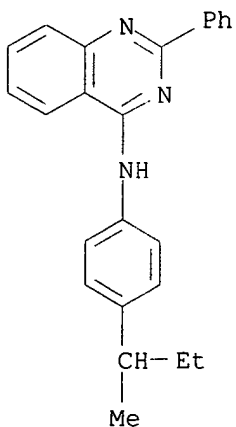
RN 474289-70-8 HCAPLUS

CN Benzonitrile, 3-[(2-phenyl-4-quinazolinyl)amino]- (9CI) (CA INDEX NAME)



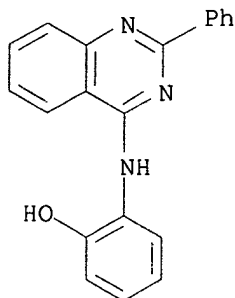
RN 474289-79-7 HCAPLUS

CN 4-Quinazolinamine, N-[4-(1-methylpropyl)phenyl]-2-phenyl- (9CI) (CA INDEX NAME)



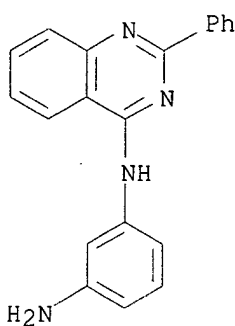
RN 474289-93-5 HCAPLUS

CN Phenol, 2-[(2-phenyl-4-quinazolinyl)amino]- (9CI) (CA INDEX NAME)



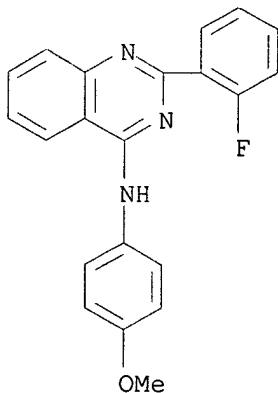
RN 474289-95-7 HCAPLUS

CN 1,3-Benzenediamine, N-(2-phenyl-4-quinazolinyl)- (9CI) (CA INDEX NAME)



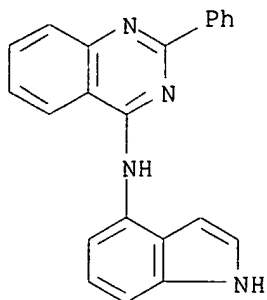
RN 474290-15-8 HCAPLUS

CN 4-Quinazolinamine, 2-(2-fluorophenyl)-N-(4-methoxyphenyl)- (9CI) (CA INDEX NAME)

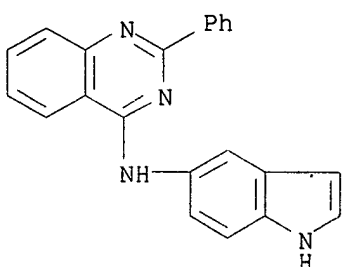


RN 474290-23-8 HCAPLUS

CN 4-Quinazolinamine, N-1H-indol-4-yl-2-phenyl- (9CI) (CA INDEX NAME)



RN 474290-26-1 HCAPLUS  
 CN 4-Quinazolinamine, N-1H-indol-5-yl-2-phenyl- (9CI) (CA INDEX NAME)



IT 289898-51-7, JNK1  
 RL: BSU (Biological study, unclassified); BIOL (Biological study)  
 (inhibition of; prepn. of quinazolines as TGF-.beta. and/or p38-.alpha.  
 kinase inhibitors)  
 RN 289898-51-7 HCAPLUS  
 CN Kinase (phosphorylating), gene c-jun protein N-terminal, 1 (9CI) (CA  
 INDEX NAME)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

REFERENCE COUNT: 80 THERE ARE 80 CITED REFERENCES AVAILABLE FOR THIS  
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 2 OF 9 HCAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2002:523279 HCAPLUS  
 DOCUMENT NUMBER: 137:242433  
 TITLE: Vitamin D inhibits the activation of stress-activated  
 protein kinases by physiological and environmental  
 stresses in keratinocytes  
 AUTHOR(S): Ravid, A.; Rubinstein, E.; Gamady, A.; Rotem, C.;  
 Liberman, U. A.; Koren, R.  
 CORPORATE SOURCE: Basil and Gerald Felsenstein Medical Research Center,  
 Sackler Faculty of Medicine, Tel Aviv University,  
 Petah Tikva, 49100, Israel  
 SOURCE: Journal of Endocrinology (2002), 173(3), 525-532  
 CODEN: JOENAK; ISSN: 0022-0795  
 PUBLISHER: Society for Endocrinology  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

AB In addn. to its known effects on keratinocyte proliferation and  
 differentiation, the hormonal form of vitamin D, 1,25-dihydroxyvitamin D3  
 (1,25(OH)2D3), has been shown to protect keratinocytes from UV- and  
 chemotherapy-induced damage. Epidermal keratinocytes contain both the  
 machinery needed to produce 1,25(OH)2D3 and vitamin D receptors. The  
 activation of the stress-activated protein kinases (SAPKs), such as

*had  
date*



FAMILY ACC. NUM. COUNT: 1

## PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002000183	A2	20020103	WO 2001-US41154	20010626
W: AE, AG, AL, AU, BA, BB, BG, BR, BZ, CA, CN, CR, CU, CZ, DM, DZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MD, MG, MK, MN, MX, NO, NZ, PL, PT, RO, SG, SI, SK, TR, TT, UA, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2002012641	A1	20020131	US 2001-891881	20010626
EP 1294349	A2	20030326	EP 2001-951098	20010626
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

## PRIORITY APPLN. INFO.:

US 2000-213940P P 20000626

WO 2001-US41154 W 20010626

AB Photoaging of human skin, such as evidenced by the increased presence of matrix metalloproteinases after exposure to UV radiation, is prevented by pre-treating the skin with an inhibitor of epidermal growth factor receptor (EGF-R) prior to exposure. Such inhibitors are preferably natural, an example of which is genistein. Compns. used for such purposes preferably include an EGF-R inhibitor as well as another MMP inhibitor, such as a retinoid.

IT 155215-87-5, c-Jun kinase

RL: BSU (Biological study, unclassified); BIOL (Biological study) (use of epidermal growth factor receptor protein tyrosine kinase inhibitors for preventing photoaging in human skin by preventing induction of matrix metalloproteinases and combination with other agents such as retinoids)

RN 155215-87-5 HCAPLUS

CN Kinase (phosphorylating), gene c-jun protein N-terminal (9CI) (CA INDEX NAME)

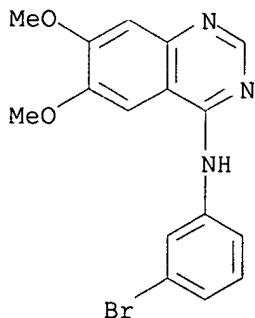
\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

IT 153436-54-5, PD 153035

RL: COS (Cosmetic use); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (use of epidermal growth factor receptor protein tyrosine kinase inhibitors for preventing photoaging in human skin by preventing induction of matrix metalloproteinases and combination with other agents such as retinoids)

RN 153436-54-5 HCAPLUS

CN 4-Quinazolinamine, N-(3-bromophenyl)-6,7-dimethoxy- (9CI) (CA INDEX NAME)



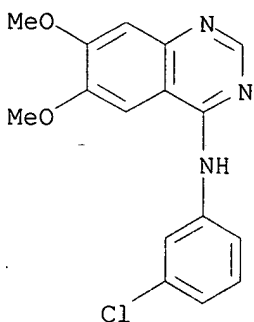
**c-Jun** N-terminal kinase (JNK) and p38, is an early cellular response to stress signals and an important determinant of cell fate. This study examines whether modulation of these SAPKs is assocd. with the effects of 1,25(OH)2D3 on keratinocytes under stress. HaCaT keratinocytes were exposed to heat shock, hyperosmotic concns. of sorbitol, the epidermal growth factor receptor tyrosine kinase inhibitor AG1487, the pro-inflammatory cytokine tumor necrosis factor .alpha., and H2O2. These stresses activated both SAPKs. Pretreatment with 1,25(OH)2D3 inhibited the activation of JNK by all stresses and the activation of p38 by heat shock, AG1478 and tumor necrosis factor .alpha.. Under the same conditions, treatment with 1,25(OH)2D3 protected HaCaT keratinocytes from cytotoxicity induced by exposure to H2O2 and hyperosmotic shock. The effect of 1,25(OH)2D3 was dose-dependent, already apparent at nanomolar concns., and time-dependent, maximal after a 24-h pre-incubation. We suggest that inhibition of SAPK activation may account for some of the well-documented protective effects of 1,25(OH)2D3 on epidermal cells during exposure to UV or chemotherapy and may also be related to the anti-inflammatory actions of the hormone in skin.

IT 153436-53-4, Tyrphostin AG 1478

RL: ADV (Adverse effect, including toxicity); BIOL (Biological study) (stressor; vitamin D inhibits activation of stress-activated protein kinases by physiol. and environmental stresses in keratinocytes)

RN 153436-53-4 HCAPLUS

CN 4-Quinazolinamine, N-(3-chlorophenyl)-6,7-dimethoxy- (9CI) (CA INDEX NAME)



IT 155215-87-5, **c-Jun** N-terminal kinase

RL: BSU (Biological study, unclassified); BIOL (Biological study) (vitamin D inhibits activation of stress-activated protein kinases by physiol. and environmental stresses in keratinocytes)

RN 155215-87-5 HCAPLUS

CN Kinase (phosphorylating), gene c-jun protein N-terminal (9CI) (CA INDEX NAME)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 3 OF 9 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:10244 HCAPLUS

DOCUMENT NUMBER: 136:90691

TITLE: Use of EGF-R protein tyrosine kinase inhibitors for preventing photoaging in human skin

INVENTOR(S): Voorhees, John J.; Fisher, Gary J.

PATENT ASSIGNEE(S): Regents of the University of Michigan, USA

SOURCE: PCT Int. Appl., 29 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

ACCESSION NUMBER: 2000:718482 HCAPLUS  
 DOCUMENT NUMBER: 134:50976  
 TITLE: Classification of Kinase Inhibitors Using BCUT Descriptors  
 AUTHOR(S): Pirard, Bernard; Pickett, Stephen D.  
 CORPORATE SOURCE: Aventis Pharma, Dagenham Research Centre, Dagenham Essex, RM10 7XS, UK  
 SOURCE: Journal of Chemical Information and Computer Sciences (2000), 40(6), 1431-1440  
 CODEN: JCISD8; ISSN: 0095-2338  
 PUBLISHER: American Chemical Society  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

*bad date*

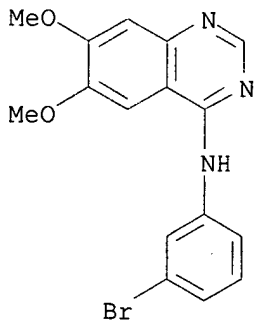
AB BCUTs are an interesting class of mol. descriptor which have been proposed for a no. of design and QSAR type tasks. It is important to understand what kind of information any particular descriptor encodes and to be able to relate this to the biol. properties of the mols. In this paper the authors present studies with BCUTs for the classification of ATP site directed kinase inhibitors active against five different protein kinases: three from the serine/threonine family and two from the tyrosine kinase family. In combination with a chemometric method, PLS discriminant anal., the BCUTs are able to correctly classify the ligands according to their target. A novel class of kinase inhibitors is correctly predicted as inhibitors of the EGFR tyrosine kinase. Comparison with other descriptor types such as two-dimensional fingerprints and three-dimensional pharmacophore-based descriptors allows the authors to gain an insight into the level of information contained within the BCUTs.

IT 153436-54-5, PD153035 171179-29-6 256521-38-7

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)  
 (classification of protein kinase inhibitors directed towards ATP site using BCUT descriptors)

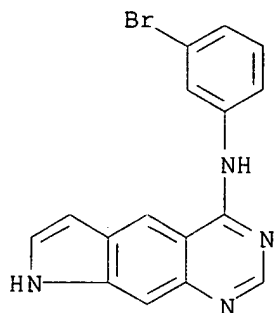
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CN 4-Quinazolinamine, N-(3-bromophenyl)-6,7-dimethoxy- (9CI) (CA INDEX NAME)

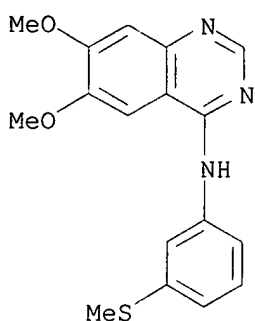


RN 171179-29-6 HCAPLUS

CN 8H-Pyrrolo[3,2-g]quinazolin-4-amine, N-(3-bromophenyl)- (9CI) (CA INDEX NAME)



RN 256521-38-7 HCAPLUS  
 CN 4-Quinazolinamine, 6,7-dimethoxy-N-[3-(methylthio)phenyl]- (9CI) (CA INDEX NAME)



IT **289898-51-7**, JNK1 kinase  
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
 (classification of protein kinase inhibitors directed towards ATP site using BCUT descriptors)  
 RN 289898-51-7 HCAPLUS  
 CN Kinase (phosphorylating), gene c-jun protein N-terminal, 1 (9CI) (CA INDEX NAME)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

REFERENCE COUNT: 69 THERE ARE 69 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 5 OF 9 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2000:535166 HCAPLUS

DOCUMENT NUMBER: 133:129859

TITLE: Inhibition of STAT3 signal transduction and the treatment of cancer in humans

INVENTOR(S): Jove, Richard; Dalton, William; Sebt, Said; Yu, Hua; Heller, Richard; Jaroszeski, Mark

PATENT ASSIGNEE(S): University of South Florida, USA

SOURCE: PCT Int. Appl., 92 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000044774	A2	20000803	WO 2000-US1845	20000127

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CZ,  
DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN,  
IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG,  
MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL,  
TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG,  
KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE,  
DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF,  
CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

EP 1146869 A2 20011024 EP 2000-905724 20000127

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,  
IE, SI, LT, LV, FI, RO

PRIORITY APPLN. INFO.:

US 1999-117600P P 19990127

WO 2000-US1845 W 20000127

AB Signal Transducer and Activator of Transcription (STAT) proteins have a fundamental role cell signaling, and are activated by a large no. of cytokines and growth factors. One member of the STAT family, STAT3, has a crit. role in oncogenesis. The present invention relates generally to disruption of the pathway of STAT3 signaling in the treatment of human cancer. STAT3 activation is shown to be present in diverse tumor cell lines and tumors, to promote oncogenesis, to inhibit apoptosis, and to reduce sensitivity to chemotherapeutic agents. Inhibition of STAT3 signaling induces apoptosis specifically in tumor cell lines, and increases sensitivity to chemotherapeutic agents. The invention relates more particularly to methods, compns., means of administering such compns., and means for identifying such compns. for the inhibition of STAT3 intracellular signaling in the treatment of human cancers. Activation of STAT3, as measured EMSA, was inhibited in tumor cell lines by inhibitors of Src and Jak protein tyrosine kinases. The Jak kinase inhibitor AG490 blocked the proliferation of human mammary tumors in nude mice. Blocking of serine phosphorylation of STAT3 had similar effects.

IT 155215-87-5, c-Jun N-terminal kinase

RL: ADV (Adverse effect, including toxicity); BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); PROC (Process); USES (Uses)

(STAT3 activation by, in tumor cell lines; inhibition of STAT3 signal transduction and treatment of cancer in humans)

RN 155215-87-5 HCAPLUS

CN Kinase (phosphorylating), gene c-jun protein N-terminal (9CI) (CA INDEX NAME)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

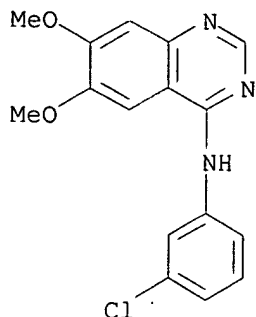
IT 153436-53-4, AG 1478

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(inhibition of STAT3 activation by, in tumor cell lines; inhibition of STAT3 signal transduction and treatment of cancer in humans)

RN 153436-53-4 HCAPLUS

CN 4-Quinazolinamine, N-(3-chlorophenyl)-6,7-dimethoxy- (9CI) (CA INDEX NAME)

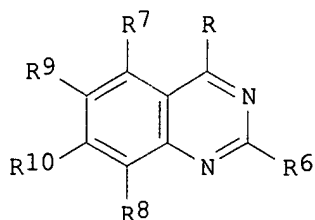


L9 ANSWER 6 OF 9 HCAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2000:15019 HCAPLUS  
 DOCUMENT NUMBER: 132:64268  
 TITLE: Preparation of 4-anilinoquinazolines and analogs as JAK3 inhibitors  
 INVENTOR(S): Uckun, Fatih M.  
 PATENT ASSIGNEE(S): Hughes Institute, USA  
 SOURCE: PCT Int. Appl., 49 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000000202	A1	20000106	WO 1999-US14923	19990630
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2337999	AA	20000106	CA 1999-2337999	19990630
AU 9948515	A1	20000117	AU 1999-48515	19990630
EP 1091739	A1	20010418	EP 1999-932145	19990630
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRIORITY APPLN. INFO.: US 1998-91150P P 19980630  
 WO 1999-US14923 W 19990630

OTHER SOURCE(S): MARPAT 132:64268  
 GI



I

AB Title compds. [I; R = ZR1; R1 = (un)substituted Ph; R6-R8 = H, halo, alkyl, alkoxy, etc.; R9,R10 = H, halo, alkyl, alkoxy, alkanoyl; R9R10 = OCH2O; Z = CHR11, O, S, NR11; R11 = H, alkyl, alkanoyl] were prepd. Thus, I (R6-R8 = H, R9 = R10 = OMe) (II; R = Cl) was aminated by 4-(HO)C6H4NH2 to give II [R = NHC6H4(OH)-4]. Data for biol. activity of I were given.

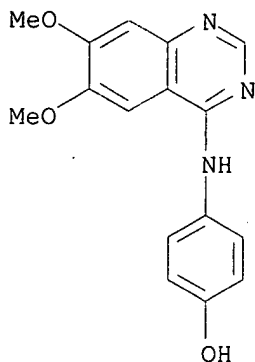
IT 202475-60-3P 211555-04-3P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of 4-anilinoquinazolines and analogs as JAK3 inhibitors)

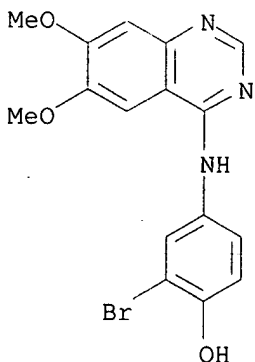
RN 202475-60-3 HCAPLUS

CN Phenol, 4-[(6,7-dimethoxy-4-quinazolinyl)amino]- (9CI) (CA INDEX NAME)



RN 211555-04-3 HCAPLUS

CN Phenol, 2-bromo-4-[(6,7-dimethoxy-4-quinazolinyl)amino]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 7 OF 9 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1999:714089 HCAPLUS

DOCUMENT NUMBER: 132:31914

TITLE: Asbestos-induced phosphorylation of epidermal growth factor receptor is linked to c-fos and apoptosis

AUTHOR(S): Zanella, Christine L.; Timblin, Cynthia R.; Cummins, Andrew; Jung, Michael; Goldberg, Jonathan; Raabe, Rachel; Tritton, Thomas R.; Mossman, Brooke T.

CORPORATE SOURCE: Department of Pathology, University of Vermont College

*\*bad date*

## SOURCE:

of Medicine, Burlington, VT, 05405, USA  
 American Journal of Physiology (1999), 277(4, Pt. 1),  
~~1684-1693~~

## PUBLISHER:

CODEN: AJPHAP; ISSN: 0002-9513

## DOCUMENT TYPE:

American Physiological Society

## LANGUAGE:

Journal

English

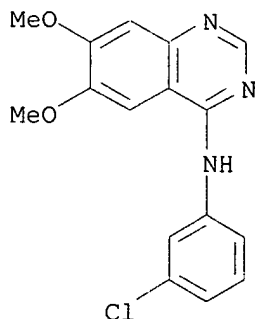
AB The authors examd. the mechanisms of interaction of crocidolite asbestos fibers with the epidermal growth factor (EGF) receptor (EGFR) and the role of the EGFR-extracellular signal-regulated kinase (ERK) signaling pathway in early-response protooncogene (c-fos/c-jun) expression and apoptosis induced by asbestos in rat pleural mesothelial (RPM) cells. Asbestos fibers, but not the nonfibrous analog riebeckite, abolished binding of EGF to the EGFR. This was not due to a direct interaction of fibers with ligand, inasmuch as binding studies using fibers and EGF in the absence of membranes showed that EGF did not adsorb to the surface of asbestos fibers. Exposure of RPM cells to asbestos caused a greater than 2-fold increase in steady-state message and protein levels of EGFR ( $P < 0.05$ ). The tyrphostin AG-1478, which inhibits the tyrosine kinase activity of the EGFR, but not the tyrphostin A-10, which does not affect EGFR activity, significantly ameliorated asbestos-induced increases in mRNA levels of c-fos but not of c-jun. Pretreatment of RPM cells with AG-1478 significantly reduced apoptosis in cells exposed to asbestos. The findings suggest that asbestos-induced binding to EGFR initiates signaling pathways responsible for increased expression of the protooncogene c-fos and the development of apoptosis. The ability to block asbestos-induced elevations in c-fos mRNA levels and apoptosis by small-mol. inhibitors of EGFR phosphorylation may have therapeutic implications in asbestos-related diseases.

IT 153436-53-4, AG-1478

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)  
 (asbestos-induced phosphorylation of epidermal growth factor receptor is linked to c-fos and apoptosis)

RN 153436-53-4 HCAPLUS

CN 4-Quinazolinamine, N-(3-chlorophenyl)-6,7-dimethoxy- (9CI) (CA INDEX NAME)



## REFERENCE COUNT:

51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 8 OF 9 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1999:659226 HCAPLUS

DOCUMENT NUMBER: 131:281600

TITLE: Methods and compositions for reducing UV-induced inhibition of collagen synthesis in human skin

INVENTOR(S): Fisher, Gary J.; Voorhees, John J.

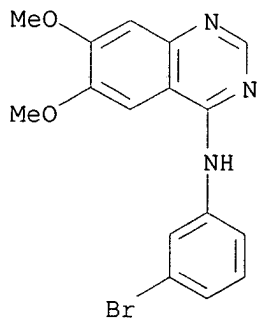
PATENT ASSIGNEE(S): The Regents of the University of Michigan, USA

SOURCE: PCT Int. Appl., 52 pp.



DOCUMENT TYPE: CODEN: PIXXD2  
 LANGUAGE: Patent  
 FAMILY ACC. NUM. COUNT: 1 English  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9951220	A1	19991014	WO 1999-US7267	19990402
W: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GD, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2326507	AA	19991014	CA 1999-2326507	19990402
AU 9936374	A1	19991025	AU 1999-36374	19990402
AU 740569	B2	20011108		
BR 9909899	A	20001226	BR 1999-9899	19990402
EP 1067920	A1	20010117	EP 1999-918456	19990402
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2002510621	T2	20020409	JP 2000-541991	19990402
PRIORITY APPLN. INFO.: US 1998-80437P P 19980402				
WO 1999-US7267 W 19990402				
*AB	Exposure of human skin to UV (UV) radiation from the sun not only induces the prodn. of enzymes (matrix metalloproteinases) that degrade collagen, but also inhibits the synthesis of new collagen by inhibiting the synthesis of procollagen. This UV-induced inhibition of the synthesis of collagen can be prevented by the topical application of a retinoid or c-JUN inhibitor to the skin prior to its exposure to UV radiation. It was shown that retinoids such as retinoic acid protect human skin in vivo against the UV-induced inhibition of collagen synthesis.			
IT	153436-54-5, PD 153035			
	RL: BSU (Biological study, unclassified); BIOL (Biological study) (ionophore or G-protein or EGF receptor antagonist; retinoids for reducing UV-induced inhibition of collagen synthesis in human skin)			
RN	153436-54-5 HCAPLUS			
CN	4-Quinazolinamine, N-(3-bromophenyl)-6,7-dimethoxy- (9CI) (CA INDEX NAME)			



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 9 OF 9 HCAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 1998:492839 HCAPLUS  
 DOCUMENT NUMBER: 129:213579  
 TITLE: Role of tyrosine kinases in induction of the c

-**jun** proto-oncogene in irradiated B-lineage lymphoid cells  
 AUTHOR(S): Goodman, Patricia A.; Niehoff, Lisa B.; Uckun, Fatih M.  
 CORPORATE SOURCE: Department of Molecular Genetics, Wayne Hughes Institute, St. Paul, MN, 55113, USA  
 SOURCE: Journal of Biological Chemistry (1998), 273(28), 17742-17748  
 CODEN: JBCHA3; ISSN: 0021-9258  
 PUBLISHER: American Society for Biochemistry and Molecular Biology  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

AB Exposure of B-lineage lymphoid cells to ionizing radiation induces an elevation of **c-jun** proto-oncogene mRNA levels. This signal is abrogated by protein-tyrosine kinase (PTK) inhibitors, indicating that activation of an as yet unidentified PTK is mandatory for radiation-induced **c-jun** expression. Here, we provide exptl. evidence that the cytoplasmic tyrosine kinases BTK, SYK, and LYN are not required for this signal. Lymphoma B-cells rendered deficient for LYN, SYK, or both by targeted gene disruption showed increased **c-jun** expression levels after radiation exposure, but the magnitude of the stimulation was lower than in wild-type cells. Thus, these PTKs may participate in the generation of an optimal signal. Notably, an inhibitor of JAK-3 (Janus family kinase-3) abrogated radiation-induced **c-jun** activation, prompting the hypothesis that a chicken homolog of JAK-3 may play a key role in initiation of the radiation-induced **c-jun** signal in B-lineage lymphoid cells.

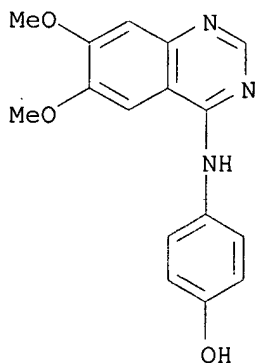
IT 202475-60-3P 211555-04-3P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)

(role of tyrosine kinases in induction of **c-jun** proto-oncogene in irradiated B-lineage lymphoid cells)

RN 202475-60-3 HCAPLUS

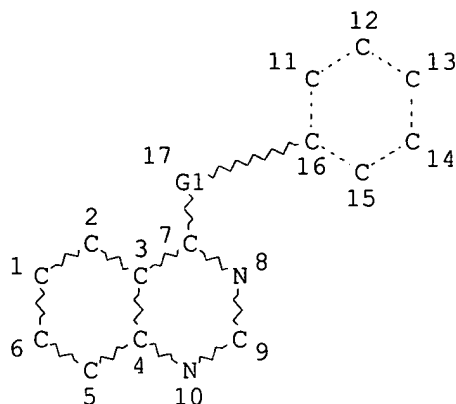
CN Phenol, 4-[(6,7-dimethoxy-4-quinazolinyl)amino]- (9CI) (CA INDEX NAME)



RN 211555-04-3 HCAPLUS

CN Phenol, 2-bromo-4-[(6,7-dimethoxy-4-quinazolinyl)amino]- (9CI) (CA INDEX NAME)

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L1 STR



VAR G1=N/S/O/C  
NODE ATTRIBUTES:  
DEFAULT MLEVEL IS ATOM  
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:  
RING(S) ARE ISOLATED OR EMBEDDED  
NUMBER OF NODES IS 17

STEREO ATTRIBUTES: NONE

L3 11589 SEA FILE=REGISTRY SSS FUL L1  
L5 15 SEA FILE=REGISTRY ABB=ON PLU=ON JANUS(L)KINASE  
L6 918 SEA FILE=HCAPLUS ABB=ON PLU=ON L3  
L8 2362 SEA FILE=HCAPLUS ABB=ON PLU=ON L5 OR JANUS(2A)KINASE  
L10 23 SEA FILE=HCAPLUS ABB=ON PLU=ON L6 AND L8

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=>

=> d ibib abs hitstr 110 1-23

L10 ANSWER 1 OF 23 HCAPLUS COPYRIGHT 2003 ACS  
ACCESSION NUMBER: 2002:764209 HCAPLUS  
DOCUMENT NUMBER: 138:20416  
TITLE: Jak3-regulated genes: DNA array analysis of  
concanavalin A-interleukin-2-activated chicken T cells  
treated with a specific Jak3 inhibitor  
AUTHOR(S): Kampa, Dione; Burnside, Joan  
CORPORATE SOURCE: Department of Chemistry and Biochemistry, University  
of Delaware, Newark, 19711, Germany  
SOURCE: Journal of Interferon and Cytokine Research (2002),  
22(9), 975-980  
CODEN: JICRFJ; ISSN: 1079-9907  
PUBLISHER: Mary Ann Liebert, Inc.  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB **Janus kinase 3 (Jak3)** is important in the activation  
and proliferation of lymphoid cells and binds to the common .gamma.  
subunit of several cytokine receptors, including the interleukin-2 (IL-2)  
receptor (IL-2R). DNA arrays were used to measure mRNA levels of a large  
no. of genes regulated by signaling through the Jak3 tyrosine kinase  
pathway by blocking Con A (ConA)-IL-2-activated chicken splenic T cells  
with a specific Jak3 inhibitor (WHI-P154). Of the 635 genes detected by

arrays contg. about 1200 cDNAs, 12 were upregulated in control cells compared with inhibitor-treated cells, and 6 were expressed at higher levels in the inhibitor-treated group. By identifying genes that are directly or indirectly regulated by Jak3, we can gain insight into the roles of this key intermediate in avian T cell activation and further our understanding of intracellular signaling networks in the immune response.

IT 157482-36-5, **Janus kinase 3**

RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(DNA array anal. of Con A-interleukin-2-activated chicken T cells treated with a specific Jak3 inhibitor)

RN 157482-36-5 HCAPLUS

CN Kinase (phosphorylating), JAK3 protein (9CI) (CA INDEX NAME)

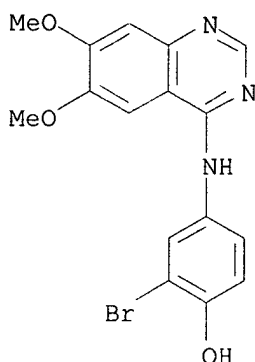
\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

IT 211555-04-3, WHI-P154

RL: BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)  
(Jak3 inhibitor; DNA array anal. of Con A-interleukin-2-activated chicken T cells treated with a specific Jak3 inhibitor)

RN 211555-04-3 HCAPLUS

CN Phenol, 2-bromo-4-[(6,7-dimethoxy-4-quinazolinyl)amino]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 2 OF 23 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:697825 HCAPLUS

DOCUMENT NUMBER: 138:248181

TITLE: Treatment of post-bone marrow transplant acute graft-versus-host disease with a rationally designed JAK3 inhibitor

AUTHOR(S): Cetkovic-Cvrlje, Marina; Roers, Bertram A.; Schonhoff, Dawn; Waurzyniak, Barbara; Liu, Xing-Ping; Uckun, Fatih M.

CORPORATE SOURCE: Experimental BMT Program, Parker Hughes Cancer Center, St. Paul, MN, 55113, USA

SOURCE: Leukemia & Lymphoma (2002), 43(7), 1447-1453  
CODEN: LELYEA; ISSN: 1042-8194

PUBLISHER: Taylor & Francis Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Here we show that the **Janus kinase 3** (JAK3) inhibitor 4-(3'-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline (JANEX-3) exhibits potent anti-GVHD activity and consequently improves the post-BMT survival outcome of C57BL/6 (H-2b) recipient mice transplanted with allogeneic bone marrow/splenocyte (BM/S) grafts from MHC disparate BALB/c mice (H-2d).

One hundred percent of the vehicle-treated allograft recipients developed severe GVHD and died with a median survival of 41 days. Treatment of recipient mice with JANEX-3 (30 mg/kg/day, 3 .times./day) after the onset of rapidly progressive severe GVHD in the 3rd week after BMT significantly improved the survival of BMT recipients with GVHD and prolonged the median survival time to 78 days ( $P < 0.0001$ , log-rank test). The probability of survival at two and three months post-BMT was  $6. \pm .6\%$  and  $0. \pm .0\%$  for vehicle-treated control mice and  $100. \pm .0\%$  and  $38. \pm .17\%$  for mice treated with JANEX-3. These results prompted the hypothesis that JAK3 plays a pivotal role in the pathophysiol. of GVHD. To test this hypothesis, we examd. if mice transplanted with allogeneic BM/S grafts from Jak3 knockout mice Jak3-/- develop GVHD. The allografts from (Jak3-/-) C57BL/6 (H-2b) mice rescued MHC-disparate recipient BALB/c mice (H-2d) of the lethal toxicity of TBI without causing fatal GVHD. Taken together, these observations establish JAK3 as a key mediator of severe GVHD after allogeneic BMT in the context of a major-HLA disparity.

IT 157482-36-5, Janus kinase 3

RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(treatment of post-bone marrow transplant acute graft-vs.-host disease  
with a rationally designed JAK3 inhibitor)

RN 157482-36-5 HCAPLUS

CN Kinase (phosphorylating), JAK3 protein (9CI) (CA INDEX NAME)

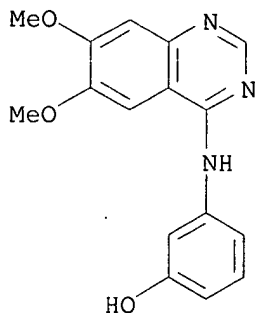
\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

IT 211555-08-7, Janex 3

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL  
(Biological study); USES (Uses)  
(treatment of post-bone marrow transplant acute graft-vs.-host disease  
with a rationally designed JAK3 inhibitor)

RN 211555-08-7 HCAPLUS

CN Phenol, 3-[(6,7-dimethoxy-4-quinazolinyl)amino]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 3 OF 23 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:636088 HCAPLUS

DOCUMENT NUMBER: 138:71823

TITLE: CD40 triggered human monocyte-derived dendritic cells  
convert to tolerogenic dendritic cells when JAK3  
activity is inhibited

AUTHOR(S): Saemann, M. D.; Kelemen, P.; Zeyda, M.; Bohmig, G.;  
Staffler, G.; Zlabinger, G. J.

CORPORATE SOURCE: Department of Internal Medicine III, Institute of  
Immunology, University of Vienna, Vienna, Austria

SOURCE: Transplantation Proceedings (2002), 34(5), 1407-1408  
CODEN: TRPPA8; ISSN: 0041-1345

PUBLISHER: Elsevier Science Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Targeting **Janus kinase 3 (JAK3)** significantly reduced CD40-triggered upregulation of the dendritic cell (DC) maturation marker CD83, costimulatory and antigen-presenting mols., resulting in an immature DC phenotype. The impairment in the allostimulatory capacity of JAK3 inhibitor-treated DC was consistent with their low costimulatory expression profile. T cells from primary MLC became hyporesponsive when restimulated with mature DC from the original donor, indicating the tolerogenic ability of JAK3 inhibitor-treated DC.

IT 157482-36-5, JAK3 kinase

RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(JAK3 kinase inhibitor disrupts CD40-mediated dendritic cell maturation and induces allograft tolerance)

RN 157482-36-5 HCAPLUS

CN Kinase (phosphorylating), JAK3 protein (9CI) (CA INDEX NAME)

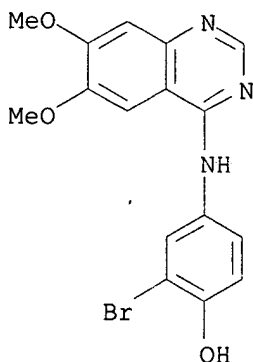
\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

IT 211555-04-3, WHI-P 154

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(JAK3 kinase inhibitor disrupts CD40-mediated dendritic cell maturation and induces allograft tolerance)

RN 211555-04-3 HCAPLUS

CN Phenol, 2-bromo-4-[(6,7-dimethoxy-4-quinazolinyl)amino]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 4 OF 23 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:418844 HCAPLUS

DOCUMENT NUMBER: 137:320073

TITLE: **Janus kinase 3 inhibitor**

WHI-P131/JANEX-1 prevents graft-versus-host disease but spares the graft-versus-leukemia function of the bone marrow allografts in a murine bone marrow transplantation model

AUTHOR(S): Uckun, Fatih M.; Roers, Bertram A.; Waurzyniak, Barbara; Liu, Xing-Ping; Cetkovic-Cvrlje, Marina

CORPORATE SOURCE: Experimental BMT Program, Parker Hughes Cancer Center and Departments of Immunology, Pathology, Chemistry, Parker Hughes Institute, St Paul, MN, USA

SOURCE: Blood (2002), 99(11), 4192-4199

CODEN: BLOOAW; ISSN: 0006-4971

PUBLISHER: American Society of Hematology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The purpose of the present study was to evaluate the effects of

graft-vs.-host disease (GVHD) prophylaxis with the **Janus kinase 3 (JAK3)** inhibitor WHI-P131/JANEX-1 on the graft-vs.-leukemic (GVL) function of marrow allografts in mice undergoing bone marrow transplantation (BMT) after being challenged with an otherwise invariably fatal dose of BCL-1 leukemia cells. GVHD prophylaxis using WHI-P131 markedly improved the survival outcome after BMT. The probability of survival at 30 days after BMT was 11%  $\pm$  6% for vehicle-treated recipients (median survival time, 25 days) vs. 63%  $\pm$  12% for recipients treated with WHI-P131 (median survival time, 36 days;  $P < .0001$ ). Because WHI-P131 is devoid of antileukemic activity against BCL-1 leukemia cells, this marked improvement in survival outcome was due to reduced incidence of GVHD-assocd. fatalities combined with sustained GVL function of the allografts in the WHI-P131 group. Notably, adoptive transfer expts. demonstrated that the spleens of WHI-P131-treated allograft recipients contained less than 0.001% BCL-1 cells. Notably, GVHD prophylaxis with WHI-P131 plus methotrexate resulted in 100% survival of mice receiving allotransplants challenged with an otherwise invariably fatal dose of BCL-1 leukemia. Taken together, our results provide strong exptl. evidence that GVHD prophylaxis using WHI-P131 does not impair the GVL function of the allografts and consequently contributes to an improved post-BMT survival outcome of the recipient mice.

IT 157482-36-5, **Janus kinase 3**

RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(**Janus kinase 3** inhibitor WHI-P131/JANEX-1 prevents graft-vs.-host disease but spares the graft-vs.-leukemia function of the bone marrow allografts in a murine bone marrow transplantation model)

RN 157482-36-5 HCAPLUS

CN Kinase (phosphorylating), JAK3 protein (9CI) (CA INDEX NAME)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

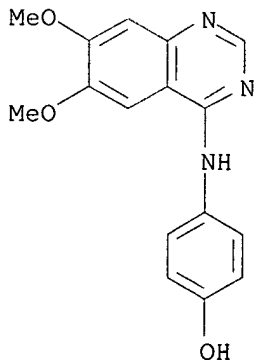
IT 202475-60-3, WHI-P131

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(**Janus kinase 3** inhibitor WHI-P131/JANEX-1 prevents graft-vs.-host disease but spares the graft-vs.-leukemia function of the bone marrow allografts in a murine bone marrow transplantation model)

RN 202475-60-3 HCAPLUS

CN Phenol, 4-[(6,7-dimethoxy-4-quinazolinyl)amino]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 5 OF 23 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:12295 HCAPLUS

DOCUMENT NUMBER: 136:272618

TITLE: CYPlA-mediated metabolism of the **Janus kinase-3** inhibitor 4-(4'-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline: structural basis for inactivation by regioselective O-demethylation

AUTHOR(S): Uckun, Fatih M.; Thoen, Jason; Chen, Hao; Sudbeck, Elise; Mao, Chen; Malaviya, Ravi; Liu, Xing-Ping; Chen, Chun-Lin

CORPORATE SOURCE: Departments of Pharmaceutical Sciences, Drug Discovery Program, Parker Hughes Cancer Center, St. Paul, MN, 55113, USA

SOURCE: Drug Metabolism and Disposition (2002), 30(1), 74-85  
CODEN: DMDSAI; ISSN: 0090-9556

PUBLISHER: American Society for Pharmacology and Experimental Therapeutics

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Here the authors report the phase I metab. of the rationally designed **Janus kinase-3** (JAK) inhibitor 4-(4'-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline (WHI-P131; JANEX-1). JANEX-1 was metabolized by the cytochrome P 450 enzymes CYP1A1 and CYP1A2 in a regioselective fashion to form the biol. inactive 7-O-demethylation product 4-(4'-hydroxyphenyl)-amino-6-methoxy-7-hydroxyquinazoline (JANEX-1-M). Our mol. modeling studies indicated that the CYP1A family enzymes bind and demethylate JANEX-1 at the C-7 position of the quinazoline ring since the alternative binding conformation with demethylation at the C-6 position would result in a severe steric clash with the binding site residues. The metab. of JANEX-1 to JANEX-1-M in pooled human liver microsomes followed Michaelis-Menten kinetics with Vmax and Km values of 34.6 pmol/min/mg and 107.3 .mu.M, resp. .alpha.-Naphthoflavone and furafylline, which both inhibit CYP1A2, significantly inhibited the formation of JANEX-1-M in human liver microsomes. There was a direct correlation between CYP1A activities and the magnitude of JANEX-1-M formation in the liver microsomes from different animal species. A significantly increased metabolic rate for JANEX-1 was obsd. in Aroclor 1254-, .beta.-naphthoflavone-, and 3-methylcholanthrene-induced microsomes but not in clofibrate-, dexamethasone-, isoniazid-, and phenobarbital-induced microsomes. The formation of JANEX-1-M in the presence of baculovirus-expressed CYP1A1 and 1A2 was consistent with Michaelis-Menten kinetics. The systemic clearance of JANEX-1-M was much faster than that of JANEX-1 (5525.1 mL/h/kg vs. 1458.0 mL/h/kg). Consequently, the area under the curve value for JANEX-1-M was much smaller than that for JANEX-1 (27.5 vs. 94.8 .mu.M .cntdot. h).

IT 157482-36-5, **Janus kinase 3**  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(CYPlA-mediated metab. of **Janus kinase-3** inhibitor  
4'-hydroxyphenyl-aminodimethoxyquinazoline and structural basis for  
inactivation by regioselective O-demethylation)

RN 157482-36-5 HCAPLUS

CN Kinase (phosphorylating), JAK3 protein (9CI) (CA INDEX NAME)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

IT 406484-24-0P

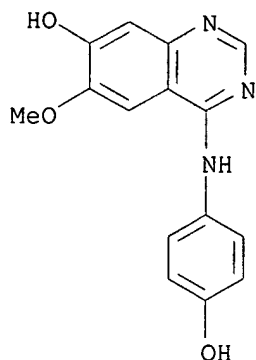
RL: BSU (Biological study, unclassified); PKT (Pharmacokinetics); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)

(CYPlA-mediated metab. of **Janus kinase-3** inhibitor  
4'-hydroxyphenyl-aminodimethoxyquinazoline and structural basis for  
inactivation by regioselective O-demethylation)

RN 406484-24-0 HCAPLUS

CN 7-Quinazolinol, 4-[(4-hydroxyphenyl)amino]-6-methoxy- (9CI) (CA INDEX NAME)



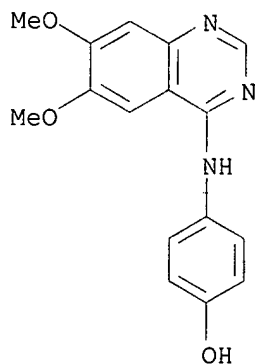


IT 202475-60-3, WHI-P131

RL: PKT (Pharmacokinetics); PRP (Properties); BIOL (Biological study)  
 (CYP1A-mediated metab. of **Janus kinase-3** inhibitor  
 4'-hydroxyphenyl-aminodimethoxyquinazoline and structural basis for  
 inactivation by regioselective O-demethylation)

RN 202475-60-3 HCAPLUS

CN Phenol, 4-[(6,7-dimethoxy-4-quinazolinyl)amino]- (9CI) (CA INDEX NAME)

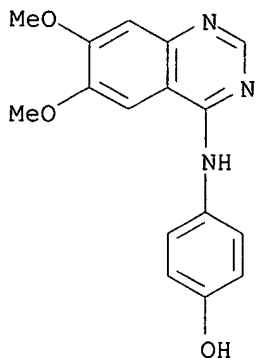


IT 188829-39-2

RL: RCT (Reactant); RACT (Reactant or reagent)  
 (CYP1A-mediated metab. of **Janus kinase-3** inhibitor  
 4'-hydroxyphenyl-aminodimethoxyquinazoline and structural basis for  
 inactivation by regioselective O-demethylation)

RN 188829-39-2 HCAPLUS

CN Phenol, 4-[(6,7-dimethoxy-4-quinazolinyl)amino]-, monohydrochloride (9CI)  
 (CA INDEX NAME)



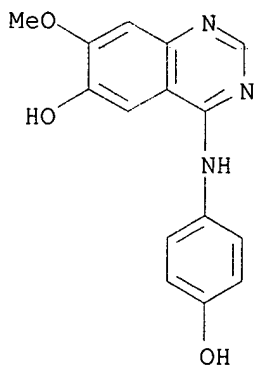
● HCl

IT 406484-25-1P

RL: SPN (Synthetic preparation); PREP (Preparation)  
 (CYP1A-mediated metab. of **Janus kinase-3** inhibitor  
 4'-hydroxyphenyl-aminodimethoxyquinazoline and structural basis for  
 inactivation by regioselective O-demethylation)

RN 406484-25-1 HCAPLUS

CN 6-Quinazolinol, 4-[(4-hydroxyphenyl)amino]-7-methoxy- (9CI) (CA INDEX  
 NAME)



REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS  
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 6 OF 23 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:545523 HCAPLUS

DOCUMENT NUMBER: 135:132432

TITLE: JAK/STAT pathway inhibitors and the uses thereof

INVENTOR(S): Vasios, George

PATENT ASSIGNEE(S): Genzyme Corporation, USA

SOURCE: PCT Int. Appl., 55 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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WO 2001052892 A2 20010726 WO 2001-US2033 20010122  
 WO 2001052892 A3 20020124

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,  
 CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,  
 HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,  
 LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU,  
 SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU,  
 ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,  
 DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,  
 BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

EP 1250137 A2 20021023 EP 2001-942563 20010122

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,  
 IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

PRIORITY APPLN. INFO.:

US 2000-177872P P 20000124

US 2000-723490 A 20001128

WO 2001-US2033 W 20010122

AB The role of JAK/STAT (**Janus Kinase**/Signal Transducers and Activators of Transcription) signal transduction pathway cellular mechanisms that lead to the onset and progression of degenerative joint diseases or disorders such as osteoarthritis (OA) is disclosed. Certain known effective OA therapeutics such as hyeminaldisine, debromohyeminaldisine, and its variants and derivs. are shown to function as JAK3-specific inhibitors, which downregulate steady state mRNA levels of key cellular components involved in cartilage degrdn. Another JAK3-specific inhibitor, not previously known as an OA therapeutic, is shown to downregulate steady state mRNA levels of various cellular components involved in cartilage degrdn. in a manner identical to that of the known OA therapeutics.

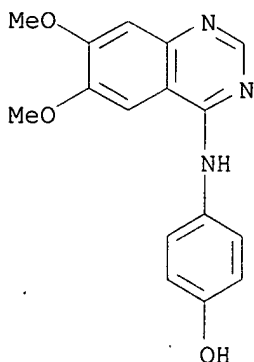
IT 202475-60-3, WHI-P131

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(aJAK/STAT pathway inhibitors for treatment of osteoarthritis)

RN 202475-60-3 HCAPLUS

CN Phenol, 4-[(6,7-dimethoxy-4-quinazolinyl)amino]- (9CI) (CA INDEX NAME)



IT 157482-36-5, Janus kinase 3

161384-16-3, Janus kinase

RL: ADV (Adverse effect, including toxicity); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(inhibitors; aJAK/STAT pathway inhibitors for treatment of osteoarthritis)

RN 157482-36-5 HCAPLUS

CN Kinase (phosphorylating), JAK3 protein (9CI) (CA INDEX NAME)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

RN 161384-16-3 HCAPLUS

CN Kinase (phosphorylating), JAK protein (9CI) (CA INDEX NAME)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

L10 ANSWER 7 OF 23 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:472434 HCAPLUS

DOCUMENT NUMBER: 135:41029

TITLE: JAK-3 inhibitors and/or inhibitors of STAT-3  
phosphorylation for inhibitors of thrombin-induced  
platelet aggregation

INVENTOR(S): Uckun, Fatih M.

PATENT ASSIGNEE(S): Parker Hughes Institute, USA

SOURCE: PCT Int. Appl., 24 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001045641	A2	20010628	WO 2000-US42345	20001129
WO 2001045641	A3	20020912		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
AU 2001049032	A5	20010703	AU 2001-49032	20001129
WO 2002043735	A1	20020606	WO 2001-US2195	20010123
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
AU 2001029722	A5	20020611	AU 2001-29722	20010123
US 2003013728	A1	20030116	US 2002-157474	20020528
PRIORITY APPLN. INFO.:			US 1999-168179P P	19991130
			WO 2000-US42345 W	20001129
			WO 2001-US2195 W	20010123

OTHER SOURCE(S): MARPAT 135:41029

AB A therapeutic method useful for treating or preventing a condition of platelet aggregation in a subject includes administering a pharmaceutically effective amt. of a compd. or compn. that inhibits JAK-3 and/or tyrosine phosphorylation of STAT-3 and inhibits thrombin-induced platelet aggregation. The condition of platelet aggregation includes hematopoietic and cerebrovascular diseases.

IT 21561-09-1, WHI-P 258

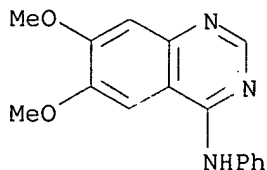
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(JAK-3 inhibitors and/or inhibitors of STAT-3 phosphorylation for

inhibitors of thrombin-induced platelet aggregation)

RN 21561-09-1 HCAPLUS

CN 4-Quinazolinamine, 6,7-dimethoxy-N-phenyl- (9CI) (CA INDEX NAME)



IT 202475-60-3, WHI-P 131 211555-04-3, WHI-P 154

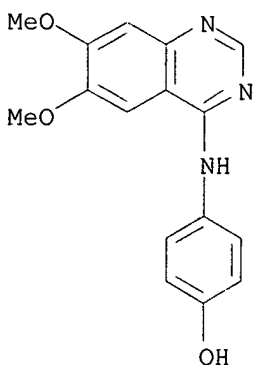
211555-05-4, WHI-P 97 211555-08-7, WHI-P 180

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(JAK-3 inhibitors and/or inhibitors of STAT-3 phosphorylation for inhibitors of thrombin-induced platelet aggregation)

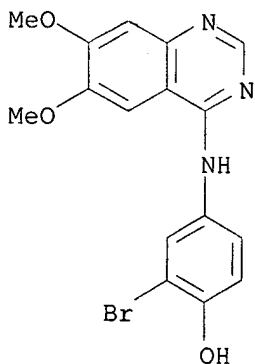
RN 202475-60-3 HCAPLUS

CN Phenol, 4-[(6,7-dimethoxy-4-quinazolinyl)amino]- (9CI) (CA INDEX NAME)



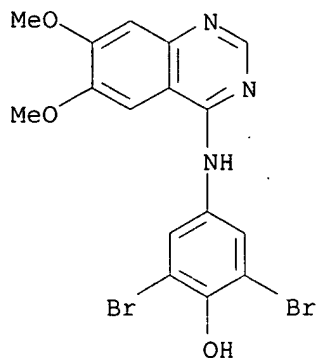
RN 211555-04-3 HCAPLUS

CN Phenol, 2-bromo-4-[(6,7-dimethoxy-4-quinazolinyl)amino]- (9CI) (CA INDEX NAME)

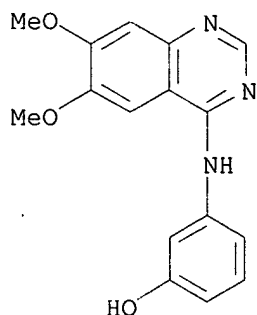


RN 211555-05-4 HCAPLUS

CN Phenol, 2,6-dibromo-4-[(6,7-dimethoxy-4-quinazolinyl)amino]- (9CI) (CA INDEX NAME)



RN 211555-08-7 HCAPLUS  
 CN Phenol, 3-[(6,7-dimethoxy-4-quinazolinyl)amino]- (9CI) (CA INDEX NAME)



IT 157482-36-5, Jak3 kinase  
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
 (JAK-3 inhibitors and/or inhibitors of STAT-3 phosphorylation for inhibitors of thrombin-induced platelet aggregation)  
 RN 157482-36-5 HCAPLUS  
 CN Kinase (phosphorylating), JAK3 protein (9CI) (CA INDEX NAME)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

L10 ANSWER 8 OF 23 HCAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2001:411480 HCAPLUS  
 DOCUMENT NUMBER: 135:221035  
 TITLE: Role of a JAK3-dependent biochemical signaling pathway in platelet activation and aggregation  
 AUTHOR(S): Tibbles, Heather E.; Vassilev, Alexei; Wendorf, Heather; Schonhoff, Dawn; Zhu, Dan; Lorenz, David; Waurzyniak, Barbara; Liu, Xing-Ping; Uckun, Fatih M.  
 CORPORATE SOURCE: Parker Hughes Cancer Center, the Departments of Hematology, Biochemistry, Parker Hughes Institute, St. Paul, MN, 55113, USA  
 SOURCE: Journal of Biological Chemistry (2001), 276(21), 17815-17822  
 CODEN: JBCHA3; ISSN: 0021-9258  
 PUBLISHER: American Society for Biochemistry and Molecular Biology  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 AB Here we provide exptl. evidence that identifies JAK3 as one of the regulators of platelet function. Treatment of platelets with thrombin.

induced tyrosine phosphorylation of the JAK3 target substrates STAT1 and STAT3. Platelets from JAK3-deficient mice displayed a decrease in tyrosine phosphorylation of STAT1 and STAT3. In accordance with these data, pretreatment of human platelets with the JAK3 inhibitor WHI-P131 markedly decreased the base-line enzymic activity of constitutively active JAK3 and abolished the thrombin-induced tyrosine phosphorylation of STAT1 and STAT3. Following thrombin stimulation, WHI-P131-treated platelets did not undergo shape changes indicative of activation such as pseudopod formation. WHI-P131 inhibited thrombin-induced degranulation/serotonin release as well as platelet aggregation. Highly effective platelet inhibitory plasma concns. of WHI-P131 were achieved in mice without toxicity. WHI-P131 prolonged the bleeding time of mice in a dose-dependent manner and improved event-free survival in a mouse model of thromboplastin-induced generalized and invariably fatal thromboembolism. To our knowledge, WHI-P131 is the first antithrombotic agent that prevents platelet aggregation by inhibiting JAK3.

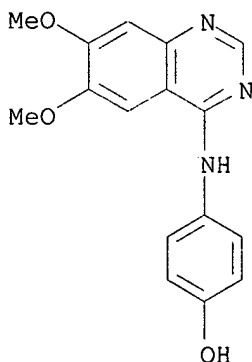
IT 202475-60-3, WHI-P131

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(role of a JAK3-dependent biochem. signaling pathway in platelet activation and aggregation)

RN 202475-60-3 HCAPLUS

CN Phenol, 4-[(6,7-dimethoxy-4-quinazolinyl)amino]- (9CI) (CA INDEX NAME)



IT 157482-36-5, JAK3 kinase

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(role of a JAK3-dependent biochem. signaling pathway in platelet activation and aggregation)

RN 157482-36-5 HCAPLUS

CN Kinase (phosphorylating), JAK3 protein (9CI) (CA INDEX NAME)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 9 OF 23 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:42652 HCAPLUS

DOCUMENT NUMBER: 134:155488

TITLE: 4-[(3-Bromo-4-hydroxyphenyl)amino]-6,7-dimethoxyquinazolin-1-ium chloride methanol solvate and 4-[(3-hydroxyphenyl)amino]-6,7-dimethoxy-1-quinazolinium chloride

AUTHOR(S): Ghosh, Sutapa; Jennissen, Jason D.; Liu, Xing Ping; Uckun, Fatih M.

CORPORATE SOURCE: Department of Structural Biology, Parker Hughes

## SOURCE:

Institute, St Paul, MN, 55113, USA  
 Acta Crystallographica, Section C: Crystal Structure  
 Communications (2001), C57(1), 76-78  
 CODEN: ACSCEE; ISSN: 0108-2701

## PUBLISHER:

Munksgaard International Publishers Ltd.

## DOCUMENT TYPE:

Journal

## LANGUAGE:

English

AB The title compds., C<sub>16</sub>H<sub>15</sub>BrN<sub>3</sub>O<sub>3</sub>+.cntdot.Cl<sup>-</sup>.cntdot.CH<sub>4</sub>O (WHI-P154) and C<sub>16</sub>H<sub>16</sub>N<sub>3</sub>O<sub>3</sub>+.cntdot.Cl<sup>-</sup> (WHI-P180), are potent inhibitors [WHI-P154 with IC<sub>50</sub> = 5.6 .mu.M and WHI-P180 with IC<sub>50</sub> = 4.0 .mu.M for epidermal growth factor receptor (EGFR) kinase inhibition] of the EGFR tyrosine kinase as well as **Janus Kinase 3**. The mol. structures of these compds. are very similar except for the dihedral angle between the anilino and quinazoline moieties which is 1.10(5).degree. for WHI-P154, and 45.66(6) and 25.29(7).degree. for the two mols. of WHI-P180 in the asym. unit. The N at the N3 position is protonated in both structures and participates in H bonding with the Cl anions. Crystallog. data are given.

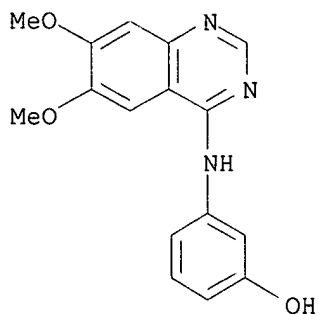
IT 153437-55-9 324035-85-0

RL: PRP (Properties)

(crystal structure of)

RN 153437-55-9 HCAPLUS

CN Phenol, 3-[(6,7-dimethoxy-4-quinazolinyl)amino]-, monohydrochloride (9CI)  
 (CA INDEX NAME)



● HCl

RN 324035-85-0 HCAPLUS

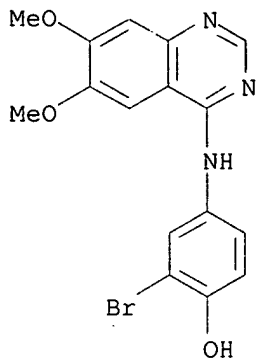
CN Phenol, 2-bromo-4-[(6,7-dimethoxy-4-quinazolinyl)amino]-, monohydrochloride, compd. with methanol (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 211555-04-3

CMF C16 H14 Br N3 O3





CM 2

CRN 67-56-1

CMF C H4 O

H<sub>3</sub>C-OH

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 10 OF 23 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2000:846101 HCAPLUS

DOCUMENT NUMBER: 134:141589

TITLE: Treatment of allergic asthma by targeting  
**Janus kinase** 3-dependent leukotriene  
synthesis in mast cells with 4-(3',5'-dibromo-4'-  
hydroxyphenyl)amino-6,7-dimethoxyquinazoline (WHI-P97)

AUTHOR(S): Malaviya, Ravi; Chen, Chun-Lin; Navara, Christopher;  
Malaviya, Rama; Liu, Xing-Ping; Keenan, Margaret;  
Waurzyniak, Barbara; Uckun, Fatih M.

CORPORATE SOURCE: Departments of Allergy and Inflammatory Diseases,  
Parker Hughes Institute, St. Paul, MN, USA

SOURCE: Journal of Pharmacology and Experimental Therapeutics  
(2000), 295(3), 912-926

CODEN: JPETAB; ISSN: 0022-3565

PUBLISHER: American Society for Pharmacology and Experimental  
Therapeutics

DOCUMENT TYPE: Journal

LANGUAGE: English

AB 4-(3',5'-Dibromo-4'-hydroxyphenyl)amino-6,7-dimethoxyquinazoline (WHI-P97) is a rationally designed potent inhibitor of **Janus kinase** (JAK)-3. Treatment of mast cells with WHI-P97 inhibited the translocation of 5-lipoxygenase (5-LO) from the nucleoplasm to the nuclear membrane and consequently 5-LO-dependent leukotriene (LT) synthesis after IgE receptor/Fc.εRI crosslinking by >90% at low micromolar concns. WHI-P97 did not directly inhibit the enzymic activity of 5-LO, but prevented its translocation to the nuclear membrane without affecting the requisite calcium signal. WHI-P97 was very well tolerated in mice, with no signs of toxicity at dose levels ranging from 5 .μg/kg to 50 mg/kg, and LD<sub>10</sub> was not reached at a 50 mg/kg dose level when administered as a single i.p. or i.v. bolus dose. Therapeutic WHI-P97 concns., which inhibit mast cell leukotriene synthesis in vitro, could easily be achieved in vivo after the i.v. or i.p. administration of a single nontoxic 40 mg/kg bolus dose of WHI-P97. Notably, WHI-P97 showed

promising biol. activity in a mouse model of allergic asthma at nontoxic dose levels. Treatment of ovalbumin-sensitized mice with WHI-P97 prevented the development of airway hyper-responsiveness to methacholine in a dose-dependent fashion. Furthermore, WHI-P97 inhibited the eosinophil recruitment to the airway lumen after the ovalbumin challenge in a dose-dependent fashion. Further development of WHI-P97 may therefore provide the basis for new and effective treatment as well as prevention programs for allergic asthma in clin. settings.

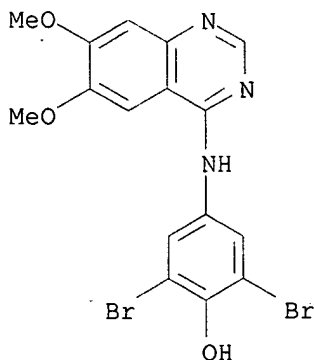
IT 211555-05-4, WHI-P 97

RL: ANT (Analyte); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PROC (Process); USES (Uses)

(treatment of allergic asthma by targeting **Janus kinase** 3-dependent leukotriene synthesis in mast cells with quinazoline WHI-P97)

RN 211555-05-4 HCAPLUS

CN Phenol, 2,6-dibromo-4-[(6,7-dimethoxy-4-quinazolinyl)amino]- (9CI) (CA INDEX NAME)



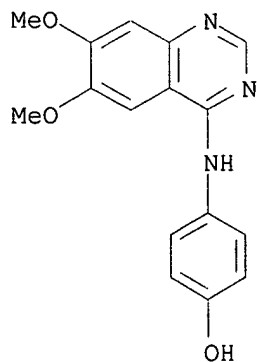
IT 202475-60-3, WHI-P131

RL: ANT (Analyte); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study)

(treatment of allergic asthma by targeting **Janus kinase** 3-dependent leukotriene synthesis in mast cells with quinazoline WHI-P97)

RN 202475-60-3 HCAPLUS

CN Phenol, 4-[(6,7-dimethoxy-4-quinazolinyl)amino]- (9CI) (CA INDEX NAME)



IT 157482-36-5, Janus kinase 3

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
 (treatment of allergic asthma by targeting **Janus kinase** 3-dependent leukotriene synthesis in mast cells with quinazoline WHI-P97)

RN 157482-36-5 HCAPLUS

CN Kinase (phosphorylating), JAK3 protein (9CI) (CA INDEX NAME)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

REFERENCE COUNT: 62 THERE ARE 62 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 11 OF 23 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2000:787792 HCAPLUS

DOCUMENT NUMBER: 133:327883

TITLE: An inhibitor of **janus kinase** 3:  
 4-(4-hydroxyphenylamino)-6,7-dimethoxyquinazolin-1-ium chloride methanol solvate

AUTHOR(S): Sudbeck, Elise A.; Jennissen, Jason D.; Liu, Xing-Ping; Uckun, Fatih M.

CORPORATE SOURCE: Drug Discovery Program, Department of Structural Biology, Parker Hughes Institute, St Paul, MN, USA  
 SOURCE: Acta Crystallographica, Section C: Crystal Structure Communications (2000), C56(10), 1282-1283  
 CODEN: ACSCEE; ISSN: 0108-2701

PUBLISHER: Munksgaard International Publishers Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The crystal structure of the title compd., C16H16N3O3+.cntdot.Cl-.cntdot.CH4O (WHI-P131, an inhibitor of **Janus kinase** 3), contains four H bonds. There are two H bonds within the asym. unit, i.e. interactions between WHI-P131 OH and Cl-, and between MeOH and Cl-. There is a 3rd interaction between WHI-P131 NH and Cl- (related by a 21 screw) and a 4th between WHI-P131 NH and MeOH (related by an n-glide). The H-bond pattern for these interactions can be described by the 1st-level H-bond graph-set notation D11(2)D11(2)D11(2)D11(2). The 2nd-level graph-set notation (for combinations of two H bonds) is D21(3)D21(3)D22(4)D22(9)D22(14)C21(9). Crystallog. data are given.

IT 303022-14-2

RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)  
 (crystal structure of **janus kinase** 3 inhibitor)

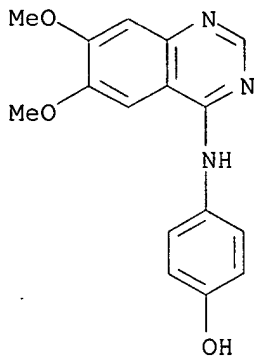
RN 303022-14-2 HCAPLUS

CN Phenol, 4-[(6,7-dimethoxy-4-quinazolinyl)amino]-, monohydrochloride, compd. with methanol (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 188829-39-2

CMF C16 H15 N3 O3 . Cl H



● HCl

CM 2

CRN 67-56-1  
CMF C H4 O

H<sub>3</sub>C-OH

REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 12 OF 23 HCAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2000:535166 HCAPLUS  
 DOCUMENT NUMBER: 133:129859  
 TITLE: Inhibition of STAT3 signal transduction and the  
 treatment of cancer in humans  
 INVENTOR(S): Jove, Richard; Dalton, William; Sebt, Said; Yu, Hua;  
 Heller, Richard; Jaroszeski, Mark  
 PATENT ASSIGNEE(S): University of South Florida, USA  
 SOURCE: PCT Int. Appl., 92 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000044774	A2	20000803	WO 2000-US1845	20000127
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1146869	A2	20011024	EP 2000-905724	20000127
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

## PRIORITY APPLN. INFO.:

US 1999-117600P P 19990127  
WO 2000-US1845 W 20000127

AB Signal Transducer and Activator of Transcription (STAT) proteins have a fundamental role cell signaling, and are activated by a large no. of cytokines and growth factors. One member of the STAT family, STAT3, has a crit. role in oncogenesis. The present invention relates generally to disruption of the pathway of STAT3 signaling in the treatment of human cancer. STAT3 activation is shown to be present in diverse tumor cell lines and tumors, to promote oncogenesis, to inhibit apoptosis, and to reduce sensitivity to chemotherapeutic agents. Inhibition of STAT3 signaling induces apoptosis specifically in tumor cell lines, and increases sensitivity to chemotherapeutic agents. The invention relates more particularly to methods, compns., means of administering such compns., and means for identifying such compns. for the inhibition of STAT3 intracellular signaling in the treatment of human cancers. Activation of STAT3, as measured EMSA, was inhibited in tumor cell lines by inhibitors of Src and Jak protein tyrosine kinases. The Jak kinase inhibitor AG490 blocked the proliferation of human mammary tumors in nude mice. Blocking of serine phosphorylation of STAT3 had similar effects.

IT 161384-16-3, Jak kinase

RL: ADV (Adverse effect, including toxicity); BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); PROC (Process); USES (Uses)

(STAT3 activation by, in tumor cell lines; inhibition of STAT3 signal transduction and treatment of cancer in humans)

RN 161384-16-3 HCAPLUS

CN Kinase (phosphorylating), JAK protein (9CI) (CA INDEX NAME)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

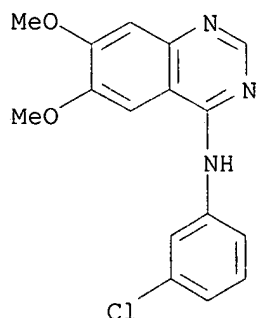
IT 153436-53-4, AG 1478

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(inhibition of STAT3 activation by, in tumor cell lines; inhibition of STAT3 signal transduction and treatment of cancer in humans)

RN 153436-53-4 HCAPLUS

CN 4-Quinazolinamine, N-(3-chlorophenyl)-6,7-dimethoxy- (9CI) (CA INDEX NAME)



L10 ANSWER 13 OF 23 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2000:433345 HCAPLUS

DOCUMENT NUMBER: 133:53698

TITLE: JAK-3 inhibitors for treating allergic disorders

INVENTOR(S): Uckun, Fatih M.; Malavia, Ravi; Sudbeck, Elise A.

PATENT ASSIGNEE(S): Hughes Institute, USA

SOURCE: U.S., 42 pp.

CODEN: USXXAM

DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6080747	A	20000627	US 1999-263420	19990305
US 6080748	A	20000627	US 1999-361491	19990726
US 6177433	B1	20010123	US 1999-443847	19991119
WO 2000051587	A2	20000908	WO 2000-US5353	20000301
WO 2000051587	A3	20001221		

*bad date*

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

EP 1158968	A2	20011205	EP 2000-913691	20000301
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R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

JP 2002538107	T2	20021112	JP 2000-602055	20000301
US 6313130	B1	20011106	US 2000-627342	20000728
US 6326373	B1	20011204	US 2000-688755	20001016
US 2002055514	A1	20020509	US 2001-791040	20010222
US 6452005	B1	20020917		
NO 2001004303	A	20010904	NO 2001-4303	20010904
US 2002165243	A1	20021107	US 2002-128683	20020423

PRIORITY APPLN. INFO.:

US 1999-263420	A1	19990305
US 1999-443847	A1	19991119
WO 2000-US5353	W	20000301
US 2000-627342	A1	20000728
US 2001-791040	A1	20010222

OTHER SOURCE(S): MARPAT 133:53698

AB Inhibitors of JAK-3 kinase for the treatment of allergy inhibit mast cell degranulation and mediator release. Quinazoline derivs. were prepd. as JAK-3 kinase inhibitors.

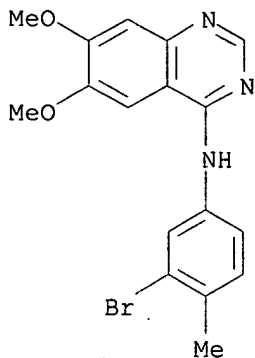
IT 211555-06-5P, WHI-P 111

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)

(WHI-P 111; prepn. of quinazoline derivs. as JAK-3 inhibitors for treating allergic disorders in relation to inhibition of mast cell degranulation and pharmacokinetics and toxicity)

RN 211555-06-5 HCAPLUS

CN 4-Quinazolinamine, N-(3-bromo-4-methylphenyl)-6,7-dimethoxy- (9CI) (CA INDEX NAME)



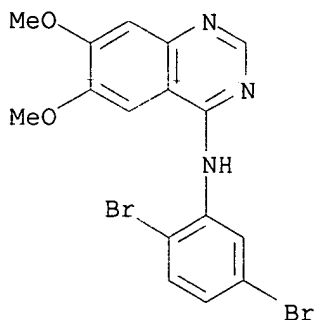
IT 247080-98-4P, WHI-P 112

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)

(WHI-P 112; prepn. of quinazoline derivs. as JAK-3 inhibitors for treating allergic disorders in relation to inhibition of mast cell degranulation and pharmacokinetics and toxicity)

RN 247080-98-4 HCAPLUS

CN 4-Quinazolinamine, N-(2,5-dibromophenyl)-6,7-dimethoxy- (9CI) (CA INDEX NAME)



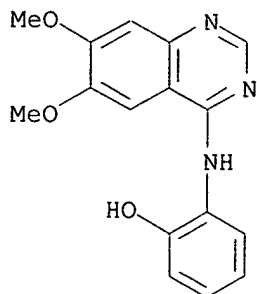
IT 211555-07-6P, WHI-P 132

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)

(WHI-P 132; prepn. of quinazoline derivs. as JAK-3 inhibitors for treating allergic disorders in relation to inhibition of mast cell degranulation and pharmacokinetics and toxicity)

RN 211555-07-6 HCAPLUS

CN Phenol, 2-[(6,7-dimethoxy-4-quinazolinyl)amino]- (9CI) (CA INDEX NAME)



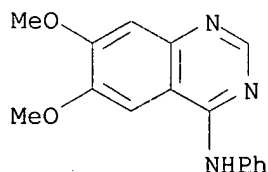
IT 21561-09-1P, WHI-P 258

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)

(WHI-P 258; prepn. of quinazoline derivs. as JAK-3 inhibitors for treating allergic disorders in relation to inhibition of mast cell degranulation and pharmacokinetics and toxicity)

RN 21561-09-1 HCAPLUS

CN 4-Quinazolinamine, 6,7-dimethoxy-N-phenyl- (9CI) (CA INDEX NAME)



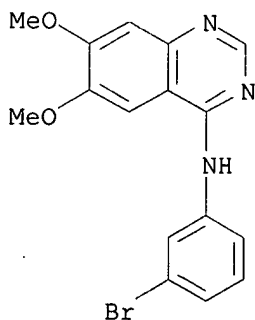
IT 153436-54-5P, WHI-P 79

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)

(WHI-P 79; prepn. of quinazoline derivs. as JAK-3 inhibitors for treating allergic disorders in relation to inhibition of mast cell degranulation and pharmacokinetics and toxicity)

RN 153436-54-5 HCAPLUS

CN 4-Quinazolinamine, N-(3-bromophenyl)-6,7-dimethoxy- (9CI) (CA INDEX NAME)



IT 211555-05-4P, WHI-P 97

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study);

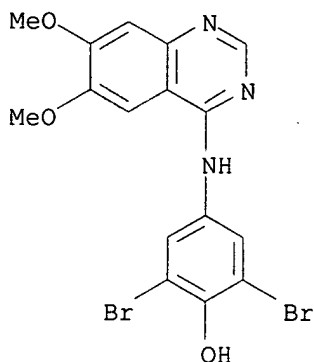


PREP (Preparation); PROC (Process); USES (Uses)

(WHI-P 97; prepn. of quinazoline derivs. as JAK-3 inhibitors for treating allergic disorders in relation to inhibition of mast cell degranulation and pharmacokinetics and toxicity)

RN 211555-05-4 HCAPLUS

CN Phenol, 2,6-dibromo-4-[(6,7-dimethoxy-4-quinazolinyl)amino]- (9CI) (CA INDEX NAME)



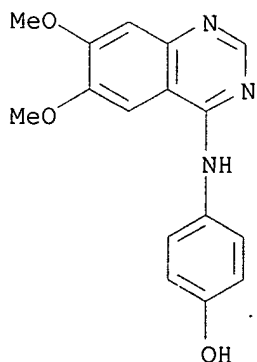
IT 202475-60-3P, WHI-P131

RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)

(prepn. of quinazoline derivs. as JAK-3 inhibitors for treating allergic disorders in relation to inhibition of mast cell degranulation and pharmacokinetics and toxicity)

RN 202475-60-3 HCAPLUS

CN Phenol, 4-[(6,7-dimethoxy-4-quinazolinyl)amino]- (9CI) (CA INDEX NAME)



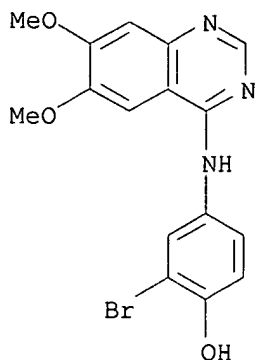
IT 211555-04-3P, WHI-P154

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)

(prepn. of quinazoline derivs. as JAK-3 inhibitors for treating allergic disorders in relation to inhibition of mast cell degranulation and pharmacokinetics and toxicity)

RN 211555-04-3 HCAPLUS

CN Phenol, 2-bromo-4-[(6,7-dimethoxy-4-quinazolinyl)amino]- (9CI) (CA INDEX NAME)

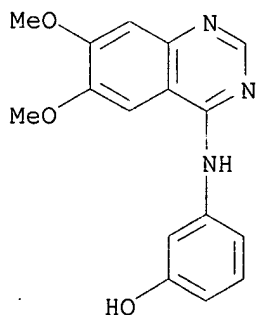


IT 211555-08-7, WHI-P180

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses) (prepn. of quinazoline derivs. as JAK-3 inhibitors for treating allergic disorders in relation to inhibition of mast cell degranulation and pharmacokinetics and toxicity)

RN 211555-08-7 HCAPLUS

CN Phenol, 3-[(6,7-dimethoxy-4-quinazolinyl)amino]- (9CI) (CA INDEX NAME)



IT 157482-36-5, JAK3 kinase

RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process) (prepn. of quinazoline derivs. as JAK-3 inhibitors for treating allergic disorders in relation to inhibition of mast cell degranulation and pharmacokinetics and toxicity)

RN 157482-36-5 HCAPLUS

CN Kinase (phosphorylating), JAK3 protein (9CI) (CA INDEX NAME)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

REFERENCE COUNT: 89 THERE ARE 89 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 14 OF 23 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2000:144864 HCAPLUS

DOCUMENT NUMBER: 132:189690

TITLE: Therapeutic uses of quinazoline derivatives as JAK-3 kinase inhibitors

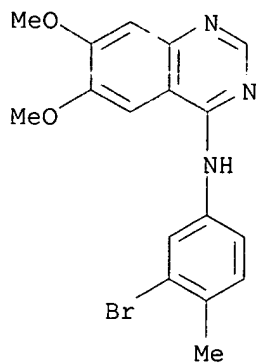
INVENTOR(S): Navara, Christopher S.; Mahajan, Sandeep; Uckun, Fatih M.

PATENT ASSIGNEE(S): Hughes Institute, USA

SOURCE: PCT Int. Appl., 131 pp.

DOCUMENT TYPE: CODEN: PIXXD2  
 LANGUAGE: Patent  
 FAMILY ACC. NUM. COUNT: 1 English  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000010981	A1	20000302	WO 1999-US19043	19990820
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2342503	AA	20000302	CA 1999-2342503	19990820
AU 9956827	A1	20000314	AU 1999-56827	19990820
EP 1105378	A1	20010613	EP 1999-943800	19990820
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
US 6313129	B1	20011106	US 1999-378093	19990820
JP 2002523403	T2	20020730	JP 2000-566255	19990820
NO 2001000887	A	20010423	NO 2001-887	20010221
US 2001044442	A1	20011122	US 2001-812098	20010319
US 6495556	B2	20021217		
US 2002042513	A1	20020411	US 2001-858824	20010516
US 6469013	B2	20021022		
PRIORITY APPLN. INFO.:				
			US 1998-97359P	P 19980821
			US 1998-97365P	P 19980821
			US 1999-378093	A1 19990820
			WO 1999-US19043	W 19990820
			US 2000-688756	A3 20001016
OTHER SOURCE(S): MARPAT 132:189690				
AB	The invention provides novel JAK-3 kinase inhibitors that are useful for treating leukemia and lymphoma. The compds. are also useful to treat or prevent skin cancer, as well as sunburn and UVB-induced skin inflammation. In addn., the compds. of the present invention prevent the immunosuppressive effects of UVB radiation, and are useful to treat or prevent autoimmune diseases, inflammation, and transplant rejection. The invention also provides pharmaceutical compns. comprising compds. of the invention, as well as therapeutic methods for their use. For example, treatments with 50 mg/kg or 75 mg/kg of a quinazoline deriv. WHI-P131 (prepn. given) were as effective as cyclosporin A treatment in prolongation of islet allograft survival in mice.			
IT	211555-06-5P, WHI-P 111			
	RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PNU (Preparation, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)			
	(WHI-P 111; therapeutic uses of quinazoline derivs. as JAK-3 kinase inhibitors)			
RN	211555-06-5 HCAPLUS			
CN	4-Quinazolinamine, N-(3-bromo-4-methylphenyl)-6,7-dimethoxy- (9CI) (CA INDEX NAME)			

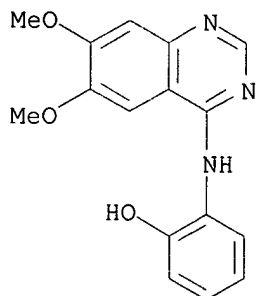


IT 211555-07-6P, WHI-P 132

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PNU (Preparation, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(WHI-P 132; therapeutic uses of quinazoline derivs. as JAK-3 kinase inhibitors)

RN 211555-07-6 HCAPLUS

CN Phenol, 2-[(6,7-dimethoxy-4-quinazolinyl)amino]- (9CI) (CA INDEX NAME)

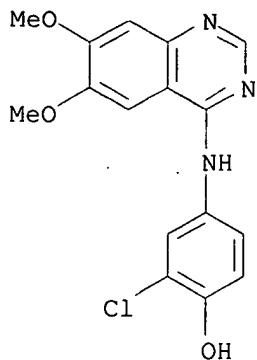


IT 211555-09-8P, WHI-P 197

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PNU (Preparation, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(WHI-P 197; therapeutic uses of quinazoline derivs. as JAK-3 kinase inhibitors)

RN 211555-09-8 HCAPLUS

CN Phenol, 2-chloro-4-[(6,7-dimethoxy-4-quinazolinyl)amino]- (9CI) (CA INDEX NAME)

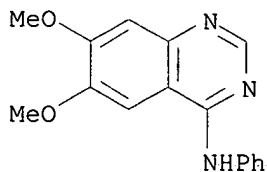


IT 21561-09-1P, WHI-P 258

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PNU (Preparation, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(WHI-P 258; therapeutic uses of quinazoline derivs. as JAK-3 kinase inhibitors)

RN 21561-09-1 HCAPLUS

CN 4-Quinazolinamine, 6,7-dimethoxy-N-phenyl- (9CI) (CA INDEX NAME)

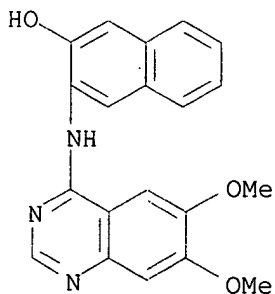


IT 251376-04-2P, WHI-P 292

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PNU (Preparation, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(WHI-P 292; therapeutic uses of quinazoline derivs. as JAK-3 kinase inhibitors)

RN 251376-04-2 HCAPLUS

CN 2-Naphthalenol, 3-[(6,7-dimethoxy-4-quinazolinyl)amino]- (9CI) (CA INDEX NAME)

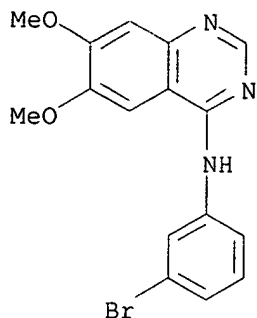


IT 153436-54-5P, WHI-P 79

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PNU (Preparation, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(WHI-P 79; therapeutic uses of quinazoline derivs. as JAK-3 kinase inhibitors)

RN 153436-54-5 HCAPLUS

CN 4-Quinazolinamine, N-(3-bromophenyl)-6,7-dimethoxy- (9CI) (CA INDEX NAME)



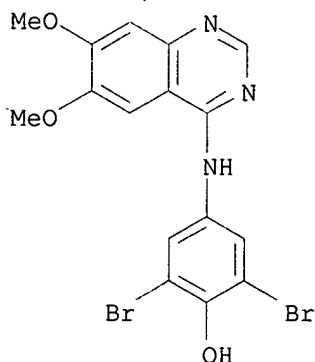
IT 211555-05-4P, WHI-P 97

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PNU (Preparation, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(WHI-P 97; therapeutic uses of quinazoline derivs. as JAK-3 kinase inhibitors)

RN 211555-05-4 HCAPLUS

CN Phenol, 2,6-dibromo-4-[(6,7-dimethoxy-4-quinazolinyl)amino]- (9CI) (CA INDEX NAME)



IT 211555-04-3P, WHI-P154 211555-08-7P, WHI-P180

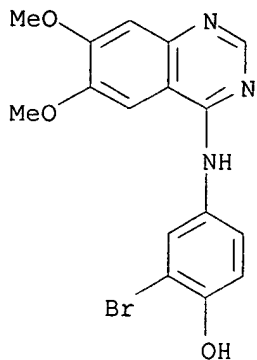
247080-98-4P, WHI-P 112

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PNU (Preparation, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

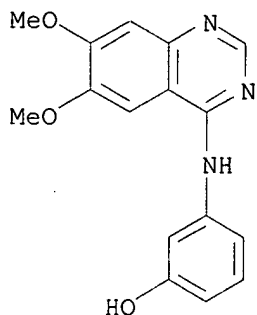
(therapeutic uses of quinazoline derivs. as JAK-3 kinase inhibitors)

RN 211555-04-3 HCAPLUS

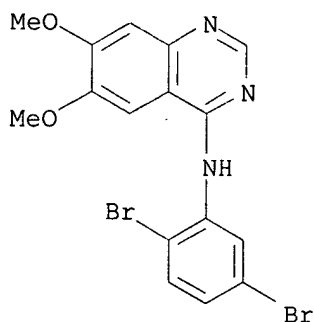
CN Phenol, 2-bromo-4-[(6,7-dimethoxy-4-quinazolinyl)amino]- (9CI) (CA INDEX NAME)



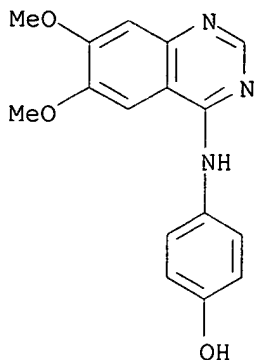
RN 211555-08-7 HCAPLUS  
 CN Phenol, 3-[(6,7-dimethoxy-4-quinazolinyl)amino]- (9CI) (CA INDEX NAME)



RN 247080-98-4 HCAPLUS  
 CN 4-Quinazolinamine, N-(2,5-dibromophenyl)-6,7-dimethoxy- (9CI) (CA INDEX NAME)



IT 202475-60-3P, WHI-P131  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (therapeutic uses of quinazoline derivs. as JAK-3 kinase inhibitors)  
 RN 202475-60-3 HCAPLUS  
 CN Phenol, 4-[(6,7-dimethoxy-4-quinazolinyl)amino]- (9CI) (CA INDEX NAME)



IT 157482-36-5, Jak3 kinase  
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
 (therapeutic uses of quinazoline derivs. as JAK-3 kinase inhibitors)  
 RN 157482-36-5 HCAPLUS  
 CN Kinase (phosphorylating), JAK3 protein (9CI) (CA INDEX NAME)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 15 OF 23 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2000:54949 HCAPLUS

DOCUMENT NUMBER: 132:329420

TITLE: Specificity of .alpha.-cyano-.beta.-hydroxy-.beta.-methyl-N-[4-(trifluoromethoxy)phenyl]-p ropenamide as an inhibitor of the epidermal growth factor receptor tyrosine kinase

AUTHOR(S): Ghosh, Sutapa; Zheng, Yaguo; Jun, Xiao; Mahajan, Sandeep; Mao, Chen; Sudbeck, Elise A.; Uckun, Fatih M.  
 CORPORATE SOURCE: Parker Hughes Cancer Center, Departments of Structural Biology, Hughes Institute, St. Paul, MN, 55113, USA

SOURCE: Clinical Cancer Research (1999), 5(12), 4264-4272  
 CODEN: CCREF4; ISSN: 1078-0432

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal

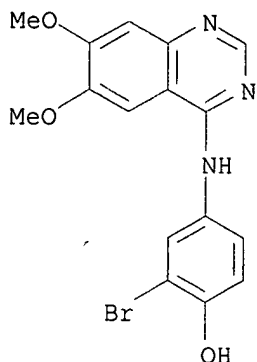
LANGUAGE: English

AB The epidermal growth factor receptor (EGFR) tyrosine kinase has an essential function for the survival of human breast cancer cells. In a systematic effort to design potent and specific inhibitors of this receptor family protein tyrosine kinase (PTK) as antibreast cancer agents, we recently reported the construction of a three-dimensional homol. model of the EGFR kinase domain. In this model, the catalytic site is defined by two .beta.-sheets that form an interface at the cleft between the NH2-terminal and COOH-terminal lobes of the kinase domain. Our modeling studies revealed a distinct, remarkably planar triangular binding pocket within the kinase domain with approx. dimensions of 15 .ANG. .times. 12.ANG. .times. 12.ANG., and the thickness of the binding pocket is .apprx.7.ANG. with an estd. vol. of .apprx.600 .ANG.3 available for inhibitor binding. Mol. docking studies had identified .alpha.-cyano-.beta.-hydroxy-.beta.-methyl-N-[4-(trifluoromethoxy)phenyl]-p ropenamide (LFM-A12) as our lead inhibitor, with an estd. binding const. of 13 .mu.M, which subsequently inhibited EGFR kinase in vitro with an IC50 value of 1.7 .mu.M. LFM-A12 was also discovered to be a highly specific inhibitor of the EGFR. Even at very high concns. ranging from 175-350 .mu.M, this inhibitor did not affect the enzymic activity of other PTKs, including the Janus kinases JAK1 and JAK3, the



Src family kinase HCK, the Tec family member Bruton's tyrosine kinase, SYK kinase, and the receptor family PTK insulin receptor kinase. This observation is in contrast to the activity of a quinazoline inhibitor tested as a control, 4-(3-bromo, 4-hydroxyanilino)-6,7-dimethoxyquinazoline, which was shown to inhibit EGFR and other tyrosine kinases such as HCK, JAK3, and SYK.

IT 211555-04-3, WHI-P154  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (epidermal growth factor receptor tyrosine kinase inhibitor LFM-A12)  
 RN 211555-04-3 HCAPLUS  
 CN Phenol, 2-bromo-4-[(6,7-dimethoxy-4-quinazolinyl)amino]- (9CI) (CA INDEX NAME)



IT 152478-56-3, Janus kinase 1  
 152478-57-4, Janus kinase 2  
 157482-36-5, Janus kinase 3  
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
 (epidermal growth factor receptor tyrosine kinase inhibitor LFM-A12)  
 RN 152478-56-3 HCAPLUS  
 CN Kinase (phosphorylating), JAK1 protein (9CI) (CA INDEX NAME)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

RN 152478-57-4 HCAPLUS  
 CN Kinase (phosphorylating), JAK2 protein (9CI) (CA INDEX NAME)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

RN 157482-36-5 HCAPLUS  
 CN Kinase (phosphorylating), JAK3 protein (9CI) (CA INDEX NAME)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 16 OF 23 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2000:15019 HCAPLUS

DOCUMENT NUMBER: 132:64268

TITLE: Preparation of 4-anilinoquinazolines and analogs as JAK3 inhibitors

INVENTOR(S): Uckun, Fatih M.

PATENT ASSIGNEE(S): Hughes Institute, USA

SOURCE: PCT Int. Appl., 49 pp.

CODEN: PIXXD2

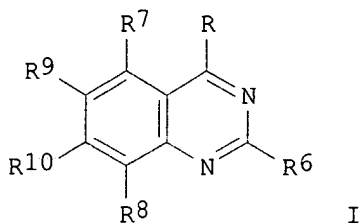
DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

## PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000000202	A1	20000106	WO 1999-US14923	19990630
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2337999	AA	20000106	CA 1999-2337999	19990630
AU 9948515	A1	20000117	AU 1999-48515	19990630
EP 1091739	A1	20010418	EP 1999-932145	19990630
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
PRIORITY APPLN. INFO.:			US 1998-91150P	P 19980630
			WO 1999-US14923	W 19990630
OTHER SOURCE(S):		MARPAT 132:64268		
GI				



AB Title compds. [I; R = ZR1; R1 = (un)substituted Ph; R6-R8 = H, halo, alkyl, alkoxy, etc.; R9, R10 = H, halo, alkyl, alkoxy, alkanoyl; R9R10 = OCH2O; Z = CHR11, O, S, NR11; R11 = H, alkyl, alkanoyl] were prepd. Thus, I (R6-R8 = H, R9 = R10 = OMe) (II; R = Cl) was aminated by 4-(HO)C6H4NH2 to give II [R = NHC6H4(OH)-4]. Data for biol. activity of I were given.

IT **157482-36-5**

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
(mediated disorders; treatment; prepn. of 4-anilinoquinazolines and analogs as JAK3 inhibitors)

RN 157482-36-5 HCAPLUS

CN Kinase (phosphorylating), JAK3 protein (9CI) (CA INDEX NAME)

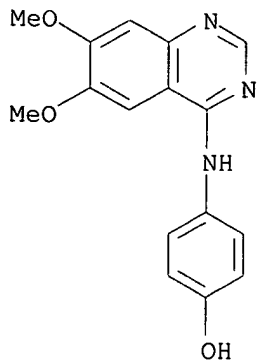
\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

IT **202475-60-3P 211555-04-3P**

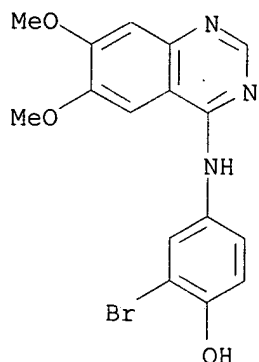
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(prepn. of 4-anilinoquinazolines and analogs as JAK3 inhibitors)

RN 202475-60-3 HCAPLUS

CN Phenol, 4-[(6,7-dimethoxy-4-quinazolinyl)amino]- (9CI) (CA INDEX NAME)



RN 211555-04-3 HCAPLUS  
 CN Phenol, 2-bromo-4-[(6,7-dimethoxy-4-quinazolinyl)amino]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 17 OF 23 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2000:12537 HCAPLUS

DOCUMENT NUMBER: 132:231841

TITLE: A Specific Inhibitor of **Janus Kinase**  
 -3 Increases Survival in a Transgenic Mouse Model of Amyotrophic Lateral Sclerosis

AUTHOR(S): Trieu, Vuong N.; Liu, Rugao; Liu, Xing-Ping; Uckun, Fatih M.

CORPORATE SOURCE: Drug Discovery Program, Hughes Institute, Roseville, MN, 55113, USA

SOURCE: Biochemical and Biophysical Research Communications (2000), 267(1), 22-25

CODEN: BBRCA9; ISSN: 0006-291X

PUBLISHER: Academic Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Amyotrophic lateral sclerosis (ALS) is a progressive, fatal neurodegenerative disorder involving the motor neurons of cortex, brain stem, and spinal cord. About 10% of all ALS patients are familial cases (FALS), of which 20% have mutations in the Cu,Zn-superoxide dismutase (SOD1) gene. The murine model for FALS, which overexpresses a FALS variant of the SOD1 gene, exhibits progressive limbic paralysis followed by death. Treatment of FALS mice with WHI-P131, a specific inhibitor of **Janus kinase 3 (JAK3)**, increased survival by more than

two months, suggesting that specific inhibitors of JAK3 may be useful in the treatment of human ALS. These results uniquely establish JAK3 as a novel mol. target for the treatment of FALS. (c) 2000 Academic Press.

IT 211555-04-3, WHI-P154 211555-05-4, WHI-P 97

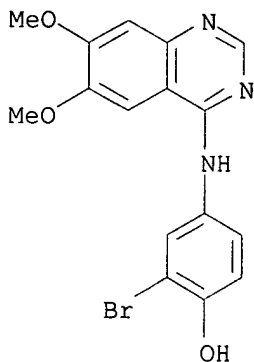
211555-06-5, WHI-P 111 211555-07-6, WHI-P 132

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(dimethoxyquinazoline inhibitors of JAK3 kinase increase survival in transgenic mouse model of amyotrophic lateral sclerosis)

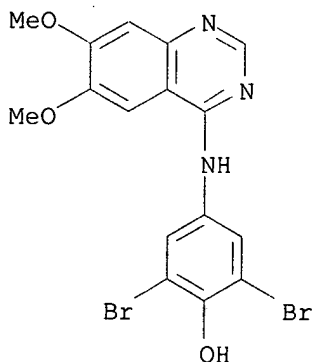
RN 211555-04-3 HCAPLUS

CN Phenol, 2-bromo-4-[(6,7-dimethoxy-4-quinazolinyl)amino]- (9CI) (CA INDEX NAME)



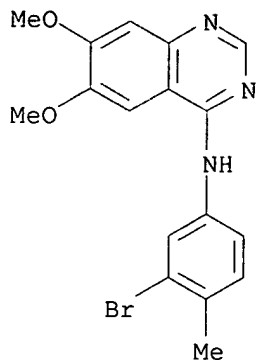
RN 211555-05-4 HCAPLUS

CN Phenol, 2,6-dibromo-4-[(6,7-dimethoxy-4-quinazolinyl)amino]- (9CI) (CA INDEX NAME)

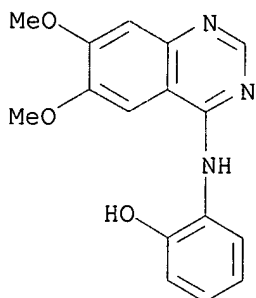


RN 211555-06-5 HCAPLUS

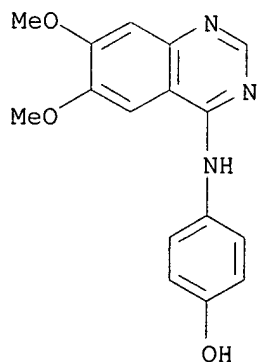
CN 4-Quinazolinamine, N-(3-bromo-4-methylphenyl)-6,7-dimethoxy- (9CI) (CA INDEX NAME)



RN 211555-07-6 HCAPLUS  
 CN Phenol, 2-[(6,7-dimethoxy-4-quinazolinyl)amino]- (9CI) (CA INDEX NAME)



IT 202475-60-3, WHI-P131  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (dimethoxyquinazoline inhibitors of JAK3 kinase increase survival in transgenic mouse model of amyotrophic lateral sclerosis)  
 RN 202475-60-3 HCAPLUS  
 CN Phenol, 4-[(6,7-dimethoxy-4-quinazolinyl)amino]- (9CI) (CA INDEX NAME)



IT 157482-36-5, Janus kinase 3  
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
 (dimethoxyquinazoline inhibitors of JAK3 kinase increase survival in transgenic mouse model of amyotrophic lateral sclerosis)

RN 157482-36-5 HCAPLUS  
 CN Kinase (phosphorylating), JAK3 protein (9CI) (CA INDEX NAME)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS  
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 18 OF 23 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1999:735691 HCAPLUS

DOCUMENT NUMBER: 132:202585

TITLE: In vivo toxicity and pharmacokinetic features of the  
**Janus kinase 3** inhibitor WHI-P131

AUTHOR(S): [4-(4'-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline]  
 Uckun, Fatih M.; Ek, Onur; Liu, Xin-Ping; Chen,  
 Chun-Lin

CORPORATE SOURCE: Parker Hughes Cancer Center, Departments of Oncology,  
 Immunology, Drug Discovery Program, Hughes Institute,  
 St. Paul, MN, 55113, USA

SOURCE: Clinical Cancer Research (1999), 5(10), 2954-2962

CODEN: CCREF4; ISSN: 1078-0432

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal

LANGUAGE: English

AB 4-(4'-Hydroxyphenyl)-amino-6,7-dimethoxyquinazoline (WHI-P131) is a potent and selective inhibitor of the **Janus kinase 3**, which triggers apoptosis in human acute lymphoblastic leukemia (ALL) cells. In this preclin. study, we evaluated the pharmacokinetics and toxicity of WHI-P131 in rats, mice, and cynomolgus monkeys. Following i.v. administration, the terminal elimination half-life of WHI-P131 was 73.2 min in rats, 103.4 min in mice, and 45.0 min in monkeys. The i.v. administered WHI-P131 showed a very wide tissue distribution in mice. Following i.p. administration, WHI-P131 was rapidly absorbed in both rats and mice, and the time to reach the max. plasma concn. (tmax) was 24.8 min in rats and 10.0 min in mice. Subsequently, WHI-P131 was eliminated with a terminal elimination half-life of 51.8 min in rats and 123.6 min in mice. The estd. i.p. bioavailability was 95% for rats, as well as for mice. WHI-P131 was quickly absorbed after oral administration in mice with a tmax of 5.8 min, but its oral bioavailability was relatively low (29.6%). The elimination half-life of WHI-P131 after oral administration was 297.6 min. WHI-P131 was not acutely toxic to mice at single i.p. bolus doses ranging from 0.5-250 mg/kg. Two cynomolgus monkeys treated with 20 mg/kg WHI-P131 and one cynomolgus monkey treated with 100 mg/kg WHI-P131 experienced no side effects. Plasma samples from WHI-P131-treated monkeys exhibited potent antileukemic activity against human ALL cells in vitro. To our knowledge, this is the first preclin. toxicity and pharmacokinetic study of a **Janus kinase 3** inhibitor. Further development of WHI-P131 may provide the basis for new and effective treatment programs for relapsed ALL in clin. settings.

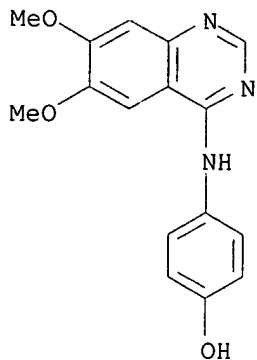
IT 202475-60-3, WHI-P131

RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)

(in vivo toxicity and pharmacokinetic features of the **Janus kinase 3** inhibitor WHI-P131)

RN 202475-60-3 HCAPLUS

CN Phenol, 4-[(6,7-dimethoxy-4-quinazolinyl)amino]- (9CI) (CA INDEX NAME)



IT 157482-36-5, Janus kinase 3

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
(in vivo toxicity and pharmacokinetic features of the Janus kinase 3 inhibitor WHI-P131)

RN 157482-36-5 HCAPLUS

CN Kinase (phosphorylating), JAK3 protein (9CI) (CA INDEX NAME)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 19 OF 23 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1999:622744 HCAPLUS

DOCUMENT NUMBER: 131:309757

TITLE: Targeting Janus kinase 3 in mast cells prevents immediate hypersensitivity reactions and anaphylaxis

AUTHOR(S): Malaviya, Ravi; Zhu, DeMin; Dibirdik, Ilker; Uckun, Fatih M.

CORPORATE SOURCE: Department of Allergy, Hughes Institute, St. Paul, MN, 55113, USA

SOURCE: Journal of Biological Chemistry (1999), 274(38), 27028-27038

CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

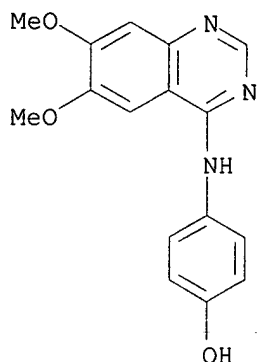
LANGUAGE: English

AB Janus kinase 3 (JAK3), a member of the Janus family protein-tyrosine kinases, is expressed in mast cells, and its enzymic activity is enhanced by IgE receptor/Fc.εRI crosslinking. Selective inhibition of JAK3 in mast cells with 4-(4'-hydroxylphenyl)-amino-6,7-dimethoxyquinazoline (WHI-P131) blocked the phospholipase C activation, calcium mobilization, and activation of microtubule-associated protein kinase after IgE receptor/Fc.εRI crosslinking. Treatment of IgE-sensitized rodent as well as human mast cells with WHI-P131 effectively inhibited the activation-associated morphological changes, degranulation, and proinflammatory mediator release after specific antigen challenge without affecting the functional integrity of the distal secretory machinery. In vivo administration of the JAK3 inhibitor WHI-P131 prevented mast cell degranulation and development of cutaneous as well as systemic fatal anaphylaxis in mice at nontoxic dose levels. Thus, JAK3 plays a pivotal role in IgE receptor/Fc.εRI-mediated mast cell responses, and targeting JAK3 with a specific inhibitor, such as WHI-P131, may provide the basis for new and effective treatment as well as prevention programs for mast cell-mediated allergic reactions.

IT 157482-36-5, JAK3 protein kinase  
 RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
 (targeting JAK3 in mast cells prevents immediate hypersensitivity reactions and anaphylaxis)  
 RN 157482-36-5 HCAPLUS  
 CN Kinase (phosphorylating), JAK3 protein (9CI) (CA INDEX NAME)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

IT 202475-60-3, WHI-P131  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (targeting JAK3 in mast cells prevents immediate hypersensitivity reactions and anaphylaxis)  
 RN 202475-60-3 HCAPLUS  
 CN Phenol, 4-[(6,7-dimethoxy-4-quinazolinyl)amino]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 20 OF 23 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1999:428003 HCAPLUS

DOCUMENT NUMBER: 131:295193

TITLE: Structure-based design of specific inhibitors of **janus kinase 3** as apoptosis-inducing antileukemic agents

AUTHOR(S): Sudbeck, Elise A.; Liu, Xing-Ping; Narla, Rama Krishna; Mahajan, Sandeep; Ghosh, Sutapa; Mao, Chen; Uckun, Fatih M.

CORPORATE SOURCE: Parker Hughes Cancer Center, Hughes Institute, St. Paul, MN, 55113, USA

SOURCE: Clinical Cancer Research (1999), 5(6), 1569-1582  
 CODEN: CCREF4; ISSN: 1078-0432

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A novel homol. model of the **kinase** domain of **Janus kinase** (JAK) 3 was used for the structure-based design of dimethoxyquinazoline compds. with potent and specific inhibitory activity against JAK3. The active site of JAK3 in this homol. model measures roughly 8 .ANG. .times. 11 .ANG. .times. 20 .ANG., with a vol. of .apprx.530 .ANG.<sup>3</sup> available for inhibitor binding. Modeling studies indicated that 4-(phenylamino)-6,7-dimethoxyquinazoline (WHI-258) (I) would likely fit into the catalytic site of JAK3 and that derivs. of I that contain an OH group at the 4' position of the Ph ring would more strongly



bind to JAK3 because of added interactions with Asp-967, a key residue in the catalytic site of JAK3. These predictions were consistent with docking studies indicating that compds. contg. a 4-OH group, WHI-P131 [4-((4-hydroxyphenyl)amino)-6,7-dimethoxyquinazoline], WHI-P154 [4-((3-bromo-4-hydroxyphenyl)amino)-6,7-dimethoxyquinazoline], and WHI-P97 [4-((3,5-dibromo-4-hydroxyphenyl)amino)-6,7-dimethoxyquinazoline], were likely to bind favorably to JAK3, with estd. Kis ranging from 0.6 to 2.3 .mu.M. These compds. inhibited JAK3 in immune complex kinase assays in a dose-dependent fashion. In contrast, compds. lacking the 4-OH group, WHI-P79 [4-((3-bromophenyl)amino)-6,7-dimethoxyquinazoline], WHI-P111 [4-((3-bromo-4-methylphenyl)amino)-6,7-dimethoxyquinazoline], WHI-P112 [4-((2,5-dibromophenyl)amino)-6,7-dimethoxyquinazoline], WHI-P132 [4-((2-hydroxyphenyl)amino)-6,7-dimethoxyquinazoline], and WHI-P258 [4-(phenylamino)-6,7-dimethoxyquinazoline], were predicted to bind less strongly, with estd. Kis ranging from 28 to 72 .mu.M. These compds. did not show any significant JAK3 inhibition in kinase assays. Furthermore, the lead dimethoxyquinazoline compd., WHI-P131, which showed potent JAK3-inhibitory activity (IC50 of 78 .mu.M), did not inhibit JAK1 and JAK2, the ZAP/SYK family tyrosine kinase SYK, the TEC family tyrosine kinase BTK, the SRC family tyrosine kinase LYN, or the receptor family tyrosine kinase insulin receptor kinase, even at concns. as high as 350 .mu.M. WHI-P131 induced apoptosis in JAK3-expressing human leukemia cell lines NALM-6 and LC1;19 but not in melanoma (M24-MET) or squamous carcinoma (SQ20B) cells. Leukemia cells were not killed by dimethoxyquinazoline compds. that were inactive against JAK3. WHI-P131 inhibited the clonogenic growth of JAK3-pos. leukemia cell lines DAUDI, RAMOS, LC1;19, NALM-6, MOLT-3, and HL-60 (but not JAK3-neg. BT-20 breast cancer, M24-MET melanoma, or SQ20B squamous carcinoma cell lines) in a concn.-dependent fashion. Potent and specific inhibitors of JAK3 such as WHI-P131 may provide the basis for the design of new treatment strategies against acute lymphoblastic leukemia, the most common form of childhood cancer.

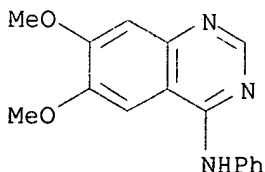
IT 21561-09-1 153436-54-5 202475-60-3, WHI-P131  
 211555-04-3, WHI-P154 211555-05-4 211555-06-5  
 211555-07-6 247080-98-4

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(structure-based design of specific inhibitors of janus  
 kinase 3 as apoptosis-inducing antileukemic agents)

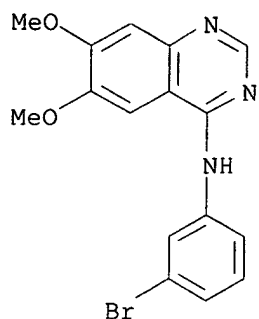
RN 21561-09-1 HCAPLUS

CN 4-Quinazolinamine, 6,7-dimethoxy-N-phenyl- (9CI) (CA INDEX NAME)



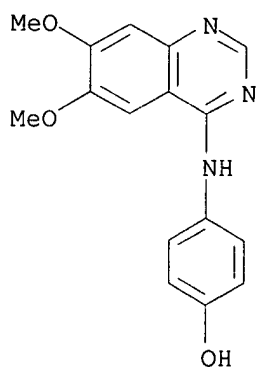
RN 153436-54-5 HCAPLUS

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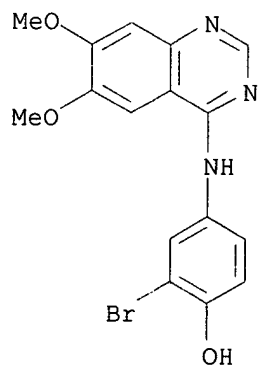
RN 202475-60-3 HCAPLUS

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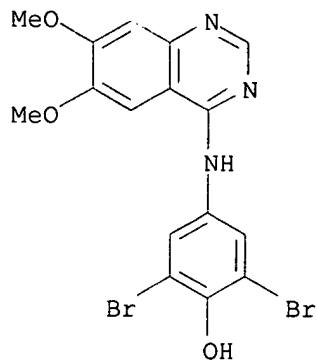
RN 211555-04-3 HCAPLUS

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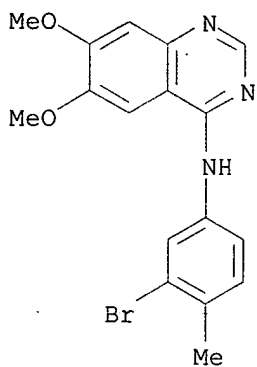


RN 211555-05-4 HCAPLUS

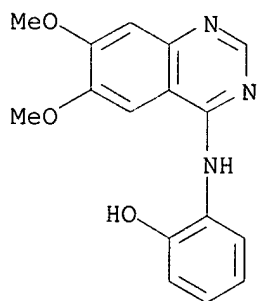
CN Phenol, 2,6-dibromo-4-[(6,7-dimethoxy-4-quinazolinyl)amino]- (9CI) (CA INDEX NAME)



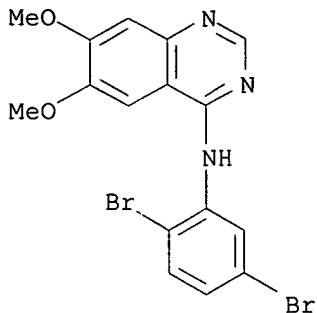
RN 211555-06-5 HCAPLUS  
 CN 4-Quinazolinamine, N-(3-bromo-4-methylphenyl)-6,7-dimethoxy- (9CI) (CA INDEX NAME)



RN 211555-07-6 HCAPLUS  
 CN Phenol, 2-[(6,7-dimethoxy-4-quinazolinyl)amino]- (9CI) (CA INDEX NAME)



RN 247080-98-4 HCAPLUS  
 CN 4-Quinazolinamine, N-(2,5-dibromophenyl)-6,7-dimethoxy- (9CI) (CA INDEX NAME)



IT 157482-36-5, JAK3 kinase  
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
 (structure-based design of specific inhibitors of **Janus kinase 3** as apoptosis-inducing antileukemic agents)  
 RN 157482-36-5 HCAPLUS  
 CN Kinase (phosphorylating), JAK3 protein (9CI) (CA INDEX NAME)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 21 OF 23 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1999:242184 HCAPLUS

DOCUMENT NUMBER: 131:72658

TITLE: Genetic and Biochemical Evidence for a Critical Role of **Janus Kinase** (JAK)-3 in Mast Cell-Mediated Type I Hypersensitivity Reactions

AUTHOR(S): Malaviya, Ravi; Uckun, Fatih M.

CORPORATE SOURCE: Department of Allergy, Hughes Institute, St. Paul, MN, USA

SOURCE: Biochemical and Biophysical Research Communications (1999), 257(3), 807-813  
 CODEN: BBRCA9; ISSN: 0006-291X

PUBLISHER: Academic Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB We investigated the role of JAK3 in IgE receptor/Fc.εRI-mediated mast cell responses. IgE/antigen induced degranulation and mediator release were substantially reduced with Jak3-/- mast cells from JAK3-null mice that were generated by targeted disruption of Jak3 gene in embryonic stem cells. Further, treatment of mast cells with (3'-bromo-4'-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline (WHI-P154), a potent inhibitor of JAK3, inhibited degranulation and proinflammatory mediator release after IgE receptor/ Fc.εRI crosslinking. Thus, JAK3 plays a pivotal role in IgE receptor/ Fc.εRI-mediated mast cell responses and targeting JAK3 may provide the basis for new and effective treatment as well as prevention programs for mast cell-mediated allergic reactions. (c) 1999 Academic Press.

IT 157482-36-5

RL: ADV (Adverse effect, including toxicity); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(genetic and biochem. evidence for crit. role of **Janus Kinase** (JAK)-3 in mast cell-mediated type I hypersensitivity reactions)

RN 157482-36-5 HCAPLUS

CN Kinase (phosphorylating), JAK3 protein (9CI) (CA INDEX NAME)

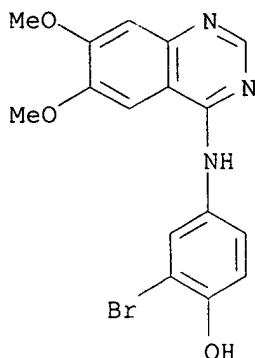
\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

IT 211555-04-3, Whi-pl54

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(genetic and biochem. evidence for crit. role of **Janus**  
**Kinase** (JAK)-3 in mast cell-mediated type I hypersensitivity  
reactions and inhibition by)

RN 211555-04-3 HCAPLUS

CN Phenol, 2-bromo-4-[(6,7-dimethoxy-4-quinazolinyl)amino]- (9CI) (CA INDEX  
NAME)



REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 22 OF 23 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1998:492839 HCAPLUS

DOCUMENT NUMBER: 129:213579

TITLE: Role of tyrosine kinases in induction of the c-jun  
proto-oncogene in irradiated B-lineage lymphoid cells  
AUTHOR(S): Goodman, Patricia A.; Niehoff, Lisa B.; Uckun, Fatih  
M.

CORPORATE SOURCE: Department of Molecular Genetics, Wayne Hughes  
Institute, St. Paul, MN, 55113, USA

SOURCE: Journal of Biological Chemistry (1998), 273(28),  
17742-17748

CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular  
Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Exposure of B-lineage lymphoid cells to ionizing radiation induces an  
elevation of c-jun proto-oncogene mRNA levels. This signal is abrogated  
by protein-tyrosine kinase (PTK) inhibitors, indicating that activation of  
an as yet unidentified PTK is mandatory for radiation-induced c-jun  
expression. Here, we provide exptl. evidence that the cytoplasmic  
tyrosine kinases BTK, SYK, and LYN are not required for this signal.  
Lymphoma B-cells rendered deficient for LYN, SYK, or both by targeted gene  
disruption showed increased c-jun expression levels after radiation  
exposure, but the magnitude of the stimulation was lower than in wild-type  
cells. Thus, these PTKs may participate in the generation of an optimal  
signal. Notably, an inhibitor of JAK-3 (**Janus** family  
**kinase-3**) abrogated radiation-induced c-jun activation, prompting  
the hypothesis that a chicken homolog of JAK-3 may play a key role in  
initiation of the radiation-induced c-jun signal in B-lineage lymphoid  
cells.

IT 202475-60-3P 211555-04-3P

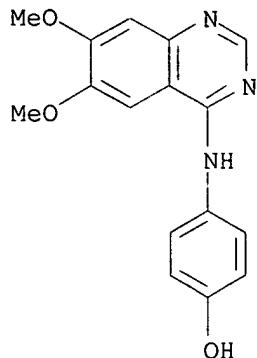
RL: BAC (Biological activity or effector, except adverse); BSU (Biological  
study, unclassified); SPN (Synthetic preparation); BIOL (Biological

study); PREP (Preparation)

(role of tyrosine kinases in induction of c-jun proto-oncogene in irradiated B-lineage lymphoid cells)

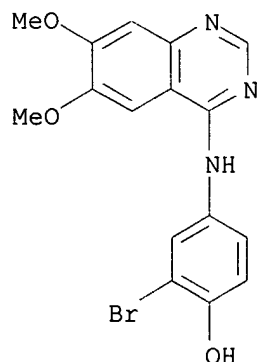
RN 202475-60-3 HCAPLUS

CN Phenol, 4-[(6,7-dimethoxy-4-quinazolinyl)amino]- (9CI) (CA INDEX NAME)



RN 211555-04-3 HCAPLUS

CN Phenol, 2-bromo-4-[(6,7-dimethoxy-4-quinazolinyl)amino]- (9CI) (CA INDEX NAME)



IT 157482-36-5, JAK-3 kinase

RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(role of tyrosine kinases in induction of c-jun proto-oncogene in irradiated B-lineage lymphoid cells)

RN 157482-36-5 HCAPLUS

CN Kinase (phosphorylating), JAK3 protein (9CI) (CA INDEX NAME)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

REFERENCE COUNT: 69 THERE ARE 69 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 23 OF 23 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1996:116898 HCAPLUS

DOCUMENT NUMBER: 124:249905

TITLE: Inhibition of acute lymphoblastic leukemia by a Jak-2 inhibitor

AUTHOR(S): Meydan, Naftaly; Grunberger, Tom; Dadi, Harjit; Shahar, Michal; Arpaia, Enrico; Lapidot, Zvi; Leeder, J. Steven; Freedman, Melvin; Cohen, Amos; et al.

CORPORATE SOURCE: The Hospital for Sick Children, Univ. Toronto, Toronto, M5G 1X8, Can.

SOURCE: Nature (London) (1996), 379(6566), 645-8  
 CODEN: NATUAS; ISSN: 0028-0836  
 PUBLISHER: Macmillan Magazines  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

AB Acute lymphoblastic leukemia (ALL) is the most common cancer of childhood. Despite the progress achieved in its treatment, 20% of cases relapse and no longer respond to chemotherapy. The most common phenotype of all cells share surface antigens with very early precursors of B cells and are therefore believed to originate from this lineage. Characterization of the growth requirement of ALL cells indicated that they were dependent on various cytokines, suggesting paracrine and/or autocrine growth regulation. Because many cytokines induce tyrosine phosphorylation in lymphoid progenitor cells, and constitutive tyrosine phosphorylation is commonly obsd. in B-lineage leukemias, attempts have been made to develop protein tyrosine kinase (PTK) blockers of leukemia cell growth. Here the authors show that leukemic cells from patients in relapse have constitutively activated Jak-2 PTK. Inhibition of Jak-2 activity by a specific tyrosine kinase blocker, AG-490, selectively blocks leukemic cell growth in vitro and in vivo by inducing programmed cell death, with no deleterious effect on normal hematopoiesis. None of the other tyrphostins tested had any activity against leukemic cells.

IT 175178-82-2, AG 1478

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(inhibition of acute lymphoblastic leukemia by a Jak-2 protein tyrosine kinase inhibitor AG-490 in relation to screening of other tyrphostins)

RN 175178-82-2 HCAPLUS

IT 152478-57-4, Jak-2 protein tyrosine kinase

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(inhibition of acute lymphoblastic leukemia by a Jak-2 protein tyrosine kinase inhibitor AG-490 in relation to screening of other tyrphostins)

RN 152478-57-4 HCAPLUS

CN Kinase (phosphorylating), JAK2 protein (9CI) (CA INDEX NAME)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

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NEWS	3	Jun 03	New e-mail delivery for search results now available
NEWS	4	Aug 08	PHARMAMarketLetter(PHARMAML) - new on STN
NEWS	5	Aug 19	Aquatic Toxicity Information Retrieval (AQUIRE) now available on STN
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NEWS	7	Sep 03	JAPIO has been reloaded and enhanced
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NEWS	9	Sep 16	CA Section Thesaurus available in CAPLUS and CA
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NEWS	11	Oct 24	BEILSTEIN adds new search fields
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NEWS	21	Feb 24	METADEX enhancements
NEWS	22	Feb 24	PCTGEN now available on STN
NEWS	23	Feb 24	TEMA now available on STN
NEWS	24	Feb 26	NTIS now allows simultaneous left and right truncation
NEWS	25	Feb 26	PCTFULL now contains images
NEWS	26	Mar 04	SDI PACKAGE for monthly delivery of multifile SDI results
NEWS	27	Mar 19	APOLLIT offering free connect time in April 2003
NEWS	28	Mar 20	EVENTLINE will be removed from STN
NEWS	29	Mar 24	PATDPAFULL now available on STN
NEWS	30	Mar 24	Additional information for trade-named substances without structures available in REGISTRY
NEWS	31	Apr 11	Display formats in DGENE enhanced
NEWS	32	Apr 14	MEDLINE Reload
NEWS	33	Apr 17	Polymer searching in REGISTRY enhanced
NEWS	34	Apr 21	Indexing from 1947 to 1956 being added to records in CA/CAPLUS
NEWS	35	Apr 21	New current-awareness alert (SDI) frequency in WPIDS/WPINDEX/WPIX



NEWS 36 Apr 28 RDISCLOSURE now available on STN  
NEWS 37 May 05 Pharmacokinetic information and systematic chemical names  
added to PHAR

NEWS EXPRESS April 4 CURRENT WINDOWS VERSION IS V6.01a, CURRENT  
MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP),  
AND CURRENT DISCOVER FILE IS DATED 01 APRIL 2003  
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L1 0 4-ANILINOQUINAZOLINES

=> s anilinoquinazoline

L2 143 ANILINOQUINAZOLINE

=> s JAK3

L3 1941 JAK3

=> s 13 and 12

L4 0 L3 AND L2

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L2 ANSWER 1 OF 143 MEDLINE

TI Mutation of Threonine 766 in the Epidermal Growth Factor Receptor Reveals a Hotspot for Resistance Formation against Selective Tyrosine Kinase Inhibitors.

AB Small molecule inhibitors of protein tyrosine kinases such as STI571 represent a major new class of therapeutics for target-selective treatment of human cancer. Clinical resistance formation to the BCR-ABL inhibitor STI571 has been observed in patients with advanced chronic myeloid leukemia and was frequently caused by a C to T single nucleotide change in the Abl kinase domain, which substituted Thr-315 with isoleucine and rendered BCR-ABL resistant to STI571 inhibition. The corresponding mutation in the epidermal growth factor receptor (EGFR) tyrosine kinase replaced Thr-766 of the EGFR by methionine and dramatically reduced the sensitivity of EGFR to inhibition by selective 4-anilinoquinazoline inhibitors such as PD153035. Inhibitor-resistant EGFR exhibited the same signaling capacity as wild-type receptor in vivo and provides a useful tool for analyzing EGFR-mediated signal transduction. Our data identify Thr-766 of the EGFR as a structural determinant that bears the potential to become a relevant feature in resistance formation during cancer therapy with EGFR-specific 4-anilinoquinazoline inhibitors.

ACCESSION NUMBER: 2003185590 IN-PROCESS

DOCUMENT NUMBER: 22590485 PubMed ID: 12594213

TITLE: Mutation of Threonine 766 in the Epidermal Growth Factor Receptor Reveals a Hotspot for Resistance Formation against Selective Tyrosine Kinase Inhibitors.

AUTHOR: Blencke Stephanie; Ullrich Axel; Daub Henrik

CORPORATE SOURCE: xxima Pharmaceuticals AG, Max-Lebsche-Platz 32, 81377 Munchen and the Department of Molecular Biology, Max-Planck-Institute of Biochemistry, Am Klopferspitz 18A, 82152 Martinsried, Germany.

SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2003 Apr 25) 278 (17) 15435-40.

Journal code: 2985121R. ISSN: 0021-9258.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals

ENTRY DATE: Entered STN: 20030422

Last Updated on STN: 20030422

L2 ANSWER 2 OF 143 MEDLINE

TI Differential responses of EGFR-/AGT-expressing cells to the "combi-triazene" SMA41.

AB PURPOSE: Previous studies have demonstrated enhanced potency associated with the binary [DNA/epidermal growth factor receptor (EGFR)] targeting properties of SMA41 (a chimeric 3-(alkyl)-1,2,3-triazene linked to a 4-anilinoquinazoline backbone) in the A431 (epidermal carcinoma of the vulva) cell line. We now report on the dependence of its antiproliferative effects (e.g. DNA damage, cell survival) on the EGFR and the DNA repair protein O6-alkylguanine DNA alkyltransferase (AGT) contents of 12 solid tumor cell lines, two of which, NIH3T3 and NIH3T3 HER14 (engineered to overexpress EGFR), were isogenic. METHODS: Receptor type specificity was determined using ELISA for competitive binding, as

well as growth factor-stimulation assays. DNA damage was studied using single-cell microelectrophoresis (comet) assays, and levels of EGFR were determined by Western blotting. The effects of SMA41 on the cell cycle of NIH3T3 cells were investigated using univariate flow cytometry. RESULTS: Studies of receptor type specificity showed that SMA41: (a) preferentially inhibited the kinase activity of EGFR over those of Src, insulin receptor and protein kinase C (PKC, a serine/threonine kinase), (b) induced stronger inhibition of growth stimulated with EGF than of growth stimulated with platelet-derived growth factor (PDGF) or fetal bovine serum (FBS). Despite the EGFR specificity of SMA41, there was an absence of a linear correlation between the EGFR status of our solid tumor cell lines and levels of DNA damage induced by the alkylating component. Similarly, EGFR levels did not correlate with IC(50) values. The antiproliferative activities of SMA41 correlated more with the AGT status of these cells and paralleled those of the clinical triazene temozolomide (TEM). However, throughout the panel, tumor cell sensitivity to SMA41 was consistently stronger than to its closest analogue TEM. Experiments performed with the isogenic cells showed that SMA41 was capable of inducing twofold higher levels of DNA damage in the EGFR transfectant and delayed cell entry to G(2)/M in both cell types. When the cells were starved and growth-stimulated with FBS (conditions under which both cell types were growth-stimulated), in contrast to TEM, SMA41 and its hydrolytic metabolite SMA52 exhibited approximately nine- and threefold stronger inhibition of growth of the EGFR transfectant. CONCLUSIONS: These results suggest that, in addition to its ability to induce DNA damage and cell cycle perturbations, SMA41 is capable of selectively targeting the cells with a growth advantage conferred by EGFR transfection. When compared with the monoalkyltriazenes prodrug TEM, its potency may be further enhanced by its ability to hydrolyze to another signal transduction inhibitor (SMA52) plus a DNA alkylating agent that may further contribute to chemosensitivity. Thus, our new "combi-targeting" strategy may well represent a tandem approach to selectively blocking receptor tyrosine kinase-mediated growth signaling while inducing significant levels of cytotoxic DNA lesions in refractory tumors.

ACCESSION NUMBER: 2002733278 MEDLINE  
DOCUMENT NUMBER: 22383620 PubMed ID: 12497201  
TITLE: Differential responses of EGFR-/AGT-expressing cells to the "combi-triazene" SMA41.  
AUTHOR: Matheson Stephanie L; McNamee James P; Jean-Claude Bertrand J  
CORPORATE SOURCE: Cancer Drug Research Laboratory, Department of Medicine, Division of Medical Oncology, McGill University Health Center/Royal Victoria Hospital, 687 Pine Avenue West, Rm. M 7.15, Montreal, Quebec, H3A 1A1, Canada.  
SOURCE: CANCER CHEMOTHERAPY AND PHARMACOLOGY, (2003 Jan) 51 (1) 11-20.  
Journal code: 7806519. ISSN: 0344-5704.  
PUB. COUNTRY: Germany: Germany, Federal Republic of  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200302  
ENTRY DATE: Entered STN: 20021227  
Last Updated on STN: 20030226  
Entered Medline: 20030225

L2 ANSWER 3 OF 143 MEDLINE  
TI Structure of the epidermal growth factor receptor kinase domain alone and in complex with a 4-anilinoquinazoline inhibitor.  
AB The crystal structure of the kinase domain from the epidermal growth factor receptor (EGFRK) including forty amino acids from the carboxyl-terminal tail has been determined to 2.6-A resolution, both with and without an EGFRK-specific inhibitor currently in Phase III clinical trials as an anti-cancer agent, erlotinib (OSI-774, CP-358,774,

Tarceva(TM)). The EGFR family members are distinguished from all other known receptor tyrosine kinases in possessing constitutive kinase activity without a phosphorylation event within their kinase domains. Despite its lack of phosphorylation, we find that the EGFRK activation loop adopts a conformation similar to that of the phosphorylated active form of the kinase domain from the insulin receptor. Surprisingly, key residues of a putative dimerization motif lying between the EGFRK domain and carboxyl-terminal substrate docking sites are found in close contact with the kinase domain. Significant intermolecular contacts involving the carboxyl-terminal tail are discussed with respect to receptor oligomerization.

ACCESSION NUMBER: 2002688134 MEDLINE  
DOCUMENT NUMBER: 22336335 PubMed ID: 12196540  
TITLE: Structure of the epidermal growth factor receptor kinase domain alone and in complex with a 4-anilinoquinazoline inhibitor.  
AUTHOR: Stamos Jennifer; Sliwkowski Mark X; Eigenbrot Charles  
CORPORATE SOURCE: Department of Protein Engineering, Genentech, Inc., South San Francisco, California 94080, USA.  
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2002 Nov 29) 277 (48) 46265-72.  
Journal code: 2985121R. ISSN: 0021-9258.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
OTHER SOURCE: PDB-1M14; PDB-1M17  
ENTRY MONTH: 200301  
ENTRY DATE: Entered STN: 20021214  
Last Updated on STN: 20030109  
Entered Medline: 20030108

L2 ANSWER 4 OF 143 MEDLINE  
TI ZD1839 (Iressa): an orally active inhibitor of epidermal growth factor signaling with potential for cancer therapy.  
AB The epidermal growth factor receptor (EGFR) is a promising target for anticancer therapy because of its role in tumor growth, metastasis and angiogenesis, and tumor resistance to chemotherapy and radiotherapy. We have developed a low-molecular-weight EGFR tyrosine kinase inhibitor (EGFR-TKI), ZD1839 (Iressa(2)). ZD1839, a substituted anilinoquinazoline, is a potent EGFR-TKI (IC(50) = 0.033 micro M) that selectively inhibits EGF-stimulated tumor cell growth (IC(50) = 0.054 micro M) and that blocks EGF-stimulated EGFR autophosphorylation in tumor cells. In studies with mice bearing a range of human tumor-derived xenografts, ZD1839 given p.o. once a day inhibited tumor growth in a dose-dependent manner. The level of expression of EGFR did not determine xenograft tumor sensitivity to ZD1839. Long-term ZD1839 (>3 months) treatment of mice bearing A431 xenografts was well tolerated, and ZD1839 completely inhibited tumor growth and induced regression of established tumors. No drug-resistant tumors appeared during ZD1839 treatment, but some tumors regrew after drug withdrawal. These studies indicate the potential utility of ZD1839 in the treatment of many human tumors and indicate that continuous once-a-day p.o. dosing might be a suitable therapeutic regimen.

ACCESSION NUMBER: 2002627047 MEDLINE  
DOCUMENT NUMBER: 22272603 PubMed ID: 12384534  
TITLE: ZD1839 (Iressa): an orally active inhibitor of epidermal growth factor signaling with potential for cancer therapy.  
AUTHOR: Wakeling Alan E; Guy Simon P; Woodburn Jim R; Ashton Susan E; Curry Brenda J; Barker Andrew J; Gibson Keith H  
CORPORATE SOURCE: Department of Cancer and Infection Research, AstraZeneca Pharmaceuticals, Alderley Park, Macclesfield, Cheshire SK10 4TG, United Kingdom.  
SOURCE: CANCER RESEARCH, (2002 Oct 15) 62 (20) 5749-54.

Journal code: 2984705R. ISSN: 0008-5472.

PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200211  
ENTRY DATE: Entered STN: 20021018  
Last Updated on STN: 20021214  
Entered Medline: 20021129

L2 ANSWER 5 OF 143 MEDLINE

TI Inhibition of epidermal growth factor receptor-mediated signaling by "Combi-triazene" BJ2000, a new probe for Combi-Targeting postulates.  
AB The Combi-Targeting concept postulates that a molecule termed combi-molecule (C-molecule) with binary epidermal growth factor receptor (EGFR) targeting/DNA-damaging properties and with the ability to be hydrolyzed to another EGFR inhibitor should induce sustained antiproliferative activity in cells overexpressing EGFR. Because we postulate that the EGFR affinity of the C-molecule and that of its hydrolytic metabolites are critical parameters for sustained potency against EGFR-overexpressing cells, we synthesized BJ2000 (IC(50) = 0.1 microM, competitive binding at ATP site), a novel C-molecule that can decompose into a 6-amino-4-anilinoquinazoline FD105 (IC(50) = 0.2 microM). Studies using the EGFR-overexpressing A431 cells revealed that BJ2000 could damage DNA and block epidermal growth factor-stimulated EGFR autophosphorylation by a partially irreversible mechanism. Blockade of EGFR autophosphorylation subsequently induced inhibition of mitogen-activated protein kinase activation and c-fos gene expression. Enzyme-linked immunosorbent assay and growth factor-mediated stimulation of proliferation assays in the EGFR-expressing NIH3T3HER14 demonstrated the preferential EGFR-targeting properties of BJ2000, and more importantly suggest that blockade of EGFR phosphorylation by this drug translate into significant growth inhibitory effects. These properties culminated into irreversible antiproliferative effects as confirmed by a sulforhodamine B assay. Five days after a 2-h treatment, BJ2000 retained significant antiproliferative effect in A431 cells, whereas its reversible metabolite FD105 almost completely lost its activity. This result in toto lend support to the Combi-Targeting concept according to which a molecular conjugate kept small enough to interact with EGFR and designed to degrade into another inhibitor of the same target plus a DNA-damaging species may induce sustained growth inhibitory effect in EGFR-overexpressing cells.

ACCESSION NUMBER: 2002482966 MEDLINE  
DOCUMENT NUMBER: 22220527 PubMed ID: 12235257  
TITLE: Inhibition of epidermal growth factor receptor-mediated signaling by "Combi-triazene" BJ2000, a new probe for Combi-Targeting postulates.  
AUTHOR: Brahimi Fouad; Matheson Stephanie L; Dudouit Fabienne; McNamee James P; Tari Ana M; Jean-Claude Bertrand J  
CORPORATE SOURCE: Cancer Drug Research Laboratory, Department of Medicine, Division of Medical Oncology, McGill University Health Center/Royal Victoria Hospital, Montreal, Quebec, Canada.  
SOURCE: JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (2002 Oct) 303 (1) 238-46.  
Journal code: 0376362. ISSN: 0022-3565.

PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200210  
ENTRY DATE: Entered STN: 20020925  
Last Updated on STN: 20021022  
Entered Medline: 20021021

L2 ANSWER 6 OF 143 MEDLINE

TI **Anilinoquinazoline** inhibitors of fructose 1,6-bisphosphatase bind at a novel allosteric site: synthesis, in vitro characterization, and X-ray crystallography.

AB The synthesis and in vitro structure-activity relationships (SAR) of a novel series of anilinoquinazolines as allosteric inhibitors of fructose-1,6-bisphosphatase (F16Bpase) are reported. The compounds have a different SAR as inhibitors of F16Bpase than anilinoquinazolines previously reported. Selective inhibition of F16Bpase can be attained through the addition of appropriate polar functional groups at the quinazoline 2-position, thus separating the F16Bpase inhibitory activity from the epidermal growth factor receptor tyrosine kinase inhibitory activity previously observed with similar structures. The compounds have been found to bind at a symmetry-repeated novel allosteric site at the subunit interface of the enzyme. Inhibition is brought about by binding to a loop comprised of residues 52-72, preventing the necessary participation of these residues in the assembly of the catalytic site. Mutagenesis studies have identified the key amino acid residues in the loop that are required for inhibitor recognition and binding.

ACCESSION NUMBER: 2002434629 MEDLINE  
DOCUMENT NUMBER: 22179131 PubMed ID: 12190310  
TITLE: **Anilinoquinazoline** inhibitors of fructose 1,6-bisphosphatase bind at a novel allosteric site: synthesis, in vitro characterization, and X-ray crystallography.

AUTHOR: Wright Stephen W; Carlo Anthony A; Carty Maynard D; Danley Dennis E; Hageman David L; Karam George A; Levy Carolyn B; Mansour Mahmoud N; Mathiowetz Alan M; McClure Lester D; Nestor Nestor B; McPherson R Kirk; Pandit Jayvardhan; Pustilnik Leslie R; Schulte Gayle K; Soeller Walter C; Treadway Judith L; Wang Ing-Kae; Bauer Paul H

CORPORATE SOURCE: Pfizer Central Research, Eastern Point Road, Groton, Connecticut 06340, USA.. [stephen\\_w\\_wright@groton.pfizer.com](mailto:stephen_w_wright@groton.pfizer.com)

SOURCE: JOURNAL OF MEDICINAL CHEMISTRY, (2002 Aug 29) 45 (18) 3865-77.  
Journal code: 9716531. ISSN: 0022-2623.

PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200209  
ENTRY DATE: Entered STN: 20020823  
Last Updated on STN: 20020924  
Entered Medline: 20020923

L2 ANSWER 7 OF 143 MEDLINE

TI Tyrosine kinase inhibitors. 17. Irreversible inhibitors of the epidermal growth factor receptor: 4-(phenylamino)quinazoline- and 4-(phenylamino)pyrido[3,2-d]pyrimidine-6-acrylamides bearing additional solubilizing functions.

AB 4-**Anilinoquinazoline**- and 4-anilinopyrido[3,2-d]pyrimidine-6-acrylamides substituted with solubilizing 7-alkylamine or 7-alkoxyamine side chains were prepared by reaction of the corresponding 6-amines with acrylic acid or acrylic acid anhydrides. In the pyrido[3,2-d]pyrimidine series, the intermediate 6-amino-7-alkylamines were prepared from 7-bromo-6-fluoropyrido[3,2-d]pyrimidine via Stille coupling with the appropriate stannane under palladium(0) catalysis. This proved a versatile method for the introduction of cationic solubilizing side chains. The compounds were evaluated for their inhibition of phosphorylation of the isolated EGFR enzyme and for inhibition of EGF-stimulated autophosphorylation of EGFR in A431 cells and of heregulin-stimulated autophosphorylation of erbB2 in MDA-MB 453 cells. Quinazoline analogues with 7-alkoxyamine solubilizing groups were potent irreversible inhibitors of the isolated EGFR enzyme, with IC<sub>50</sub>[app] values from 2 to 4 nM, and potentially inhibited both EGFR and erbB2

autophosphorylation in cells. 7-Alkylamino- and 7-alkoxyaminopyrido[3,2-d]pyrimidines were also irreversible inhibitors with equal or superior potency against the isolated enzyme but were less effective in the cellular autophosphorylation assays. Both quinazoline- and pyrido[3,2-d]pyrimidine-6-acrylamides bound at the ATP site alkylating cysteine 773, as shown by electrospray ionization mass spectrometry, and had similar rates of absorptive and secretory transport in Caco-2 cells. A comparison of two 7-propoxymorpholide analogues showed that the pyrido[3,2-d]pyrimidine-6-acrylamide had greater amide instability and higher acrylamide reactivity, being converted to glutathione adducts in cells more rapidly than the corresponding quinazoline. This difference may contribute to the observed lower cellular potency of the pyrido[3,2-d]pyrimidine-6-acrylamides. Selected compounds showed high in vivo activity against A431 xenografts on oral dosing, with the quinazolines being superior to the pyrido[3,2-d]pyrimidines. Overall, the quinazolines proved superior to previous analogues in terms of aqueous solubility, potency, and in vivo antitumor activity, and one example (CI 1033) has been selected for clinical evaluation.

ACCESSION NUMBER: 2002372739 MEDLINE  
DOCUMENT NUMBER: 21060475 PubMed ID: 10753475  
TITLE: Tyrosine kinase inhibitors. 17. Irreversible inhibitors of the epidermal growth factor receptor: 4-(phenylamino)quinazoline- and 4-(phenylamino)pyrido[3,2-d]pyrimidine-6-acrylamides bearing additional solubilizing functions.  
AUTHOR: Smaill J B; Rewcastle G W; Loo J A; Greis K D; Chan O H; Reyner E L; Lipka E; Showalter H D; Vincent P W; Elliott W L; Denny W A  
CORPORATE SOURCE: Auckland Cancer Society Research Centre, Faculty of Medical and Health Sciences, The University of Auckland, Private Bag 92019, Auckland, New Zealand.  
SOURCE: JOURNAL OF MEDICINAL CHEMISTRY, (2000 Apr 6) 43 (7) 1380-97.  
Journal code: 9716531. ISSN: 0022-2623.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200208  
ENTRY DATE: Entered STN: 20020717  
Last Updated on STN: 20020803  
Entered Medline: 20020802

L2 ANSWER 8 OF 143 MEDLINE

TI Novel 4-anilinoquinazolines with C-7 basic side chains: design and structure activity relationship of a series of potent, orally active, VEGF receptor tyrosine kinase inhibitors.

AB We have previously shown that 4-anilinoquinazolines can be potent inhibitors of vascular endothelial growth factor (VEGF) receptor (Flt-1 and KDR) tyrosine kinase activity. A novel subseries of 4-anilinoquinazolines that possess basic side chains at the C-7 position of the quinazoline nucleus have been synthesized. This subseries contains potent, nanomolar inhibitors of KDR (median IC(50) 0.02 microm, range 0.001-0.04 microm), which are comparatively less potent vs Flt-1 tyrosine kinase (median IC(50) 0.55 microm, range 0.02-1.6 microm). The compounds also retain some inhibitory activity against the tyrosine kinase associated to the endothelial growth factor receptor (EGFR) (median IC(50) 0.2 microm, range 0.075-0.8 microm) but demonstrate selectivity vs that associated to the FGF receptor 1 (median IC(50) 2.5 microm, range 0.9-19 microm). This selectivity profile is also evident in a growth factor-stimulated human endothelial cell (HUVEC) proliferation assay (i.e., inhibition of VEGF > EGF > FGF), with inhibition of VEGF-induced proliferation being achieved at nanomolar concentrations (median IC(50) 0.06 microm). Further examination of compound 2 (ZD6474) in recombinant

enzyme assays revealed excellent selectivity for the inhibition of KDR tyrosine kinase (IC(50) 0.04 microm) vs the kinase activity of erbB2, MEK, CDK-2, Tie-2, IGFR-1R, PDK, PDGFRbeta, and AKT (IC(50) range: 1.1 to >100 microm). Anilinoquinazolines possessing basic C-7 side chains exhibited markedly improved aqueous solubility over previously described anilinoquinazolines possessing neutral C-7 side chains (up to 500-fold improvement at pH 7.4). In addition, aqueous solubility of the neutral fraction present at pH 7.4 of the basic subseries of **anilinoquinazoline** proved to be higher than that of the neutral analogue 1 (ZD4190). Oral administration of representative compounds to mice (50 mg/kg) produced plasma levels between 0.2 and 3 microm at 24 h after dosing. Our development candidate 2 demonstrated a very attractive in vitro profile combined with excellent solubility (330 microm at pH 7.4) and good oral bioavailability in rat and dog (> 80 and > 50%, respectively). This compound demonstrated highly significant, dose-dependent, antitumor activity in athymic mice. Once daily oral administration of 100 mg/kg of compound 2 for 21 days inhibited the growth of established Calu-6 lung carcinoma xenografts by 79% (P < 0.001, Mann Whitney rank sum test), and substantial inhibition (36%, P < 0.02) was evident with 12.5 mg/kg/day.

ACCESSION NUMBER: 2002178113 MEDLINE  
DOCUMENT NUMBER: 21877156 PubMed ID: 11881999  
TITLE: Novel 4-anilinoquinazolines with C-7 basic side chains: design and structure activity relationship of a series of potent, orally active, VEGF receptor tyrosine kinase inhibitors.  
AUTHOR: Hennequin Laurent F; Stokes Elaine S E; Thomas Andrew P; Johnstone Craig; Ple Patrick A; Ogilvie Donald J; Dukes Michael; Wedge Stephen R; Kendrew Jane; Curwen Jon O  
CORPORATE SOURCE: AstraZeneca, Centre de Recherches, Z.I. La Pompelle, B.P. 1050, Chemin de Vrilly, 51689 Reims, Cedex 2, France.. laurent.hennequin@astrazeneca.com  
SOURCE: JOURNAL OF MEDICINAL CHEMISTRY, (2002 Mar 14) 45 (6) 1300-12.  
Journal code: 9716531. ISSN: 0022-2623.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200204  
ENTRY DATE: Entered STN: 20020326  
Last Updated on STN: 20020429  
Entered Medline: 20020426

L2 ANSWER 9 OF 143 MEDLINE  
TI ZD1839, a selective epidermal growth factor receptor tyrosine kinase inhibitor, alone and in combination with radiation and chemotherapy as a new therapeutic strategy in non-small cell lung cancer.  
AB The epidermal growth factor receptor is overexpressed in a majority of non-small cell lung cancers and has been associated with a poor prognosis. Preclinical studies have shown that ZD1839, an oral **anilinoquinazoline**, targets the epidermal growth factor receptor-associated tyrosine kinase, reversibly inhibiting critical downstream signaling and resulting in cancer cell growth arrest. Potent antitumor effects have been observed in human lung tumor xenograft models. Preclinical studies have shown additive to synergistic effects when ZD1839 is combined with radiation or chemotherapy in colon, head and neck, and non-small cell lung cancers. Phase I clinical trials have shown modest dose-related toxicity, and antitumor activity has been reported in a variety of malignancies including lung cancer. Future studies will certainly combine ZD1839 with chemotherapy or radiation. ZD1839 also may be effective as a chemoprevention agent because premalignant lesions often overexpress epidermal growth factor receptor.

ACCESSION NUMBER: 2002162345 MEDLINE



DOCUMENT NUMBER: 21891327 PubMed ID: 11894012  
TITLE: ZD1839, a selective epidermal growth factor receptor tyrosine kinase inhibitor, alone and in combination with radiation and chemotherapy as a new therapeutic strategy in non-small cell lung cancer.  
AUTHOR: Raben David; Helfrich Barbara A; Chan Dan; Johnson Gary; Bunn Paul A Jr  
CORPORATE SOURCE: Department of Radiation Oncology, University of Colorado Comprehensive Cancer Center, Denver, CO 80010-0510, USA.  
SOURCE: SEMINARS IN ONCOLOGY, (2002 Feb) 29 (1 Suppl 4) 37-46.  
Ref: 36  
Journal code: 0420432. ISSN: 0093-7754.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
General Review; (REVIEW)  
(REVIEW, TUTORIAL)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200204  
ENTRY DATE: Entered STN: 20020315  
Last Updated on STN: 20020404  
Entered Medline: 20020402

L2 ANSWER 10 OF 143 MEDLINE  
TI 1,4-dioxane-fused 4-anilinoquinazoline as inhibitors of epidermal growth factor receptor kinase.  
AB The 4-anilinoquinazoline PD 153035 (1) is a potential antitumor agent which acts by inhibiting tyrosine kinase activity of epidermal growth factor receptor (EGFR) via competitive binding at the ATP site of enzyme. A series of cyclic analogues of PD 153035 bearing the 1,4-dioxane ring was prepared by reaction of 6-chloro derivative 5 with several aniline nucleophiles. These were evaluated for their ability to inhibit the EGFR kinase and the growth of primary human tumor cell cultures. All of the new 4-anilinoquinazolines exhibited less potency than PD 153035 against EGFR kinase. However, compounds 2b, 2c, 2e, 2g, and 2h showed higher inhibitory activities than PD 153035 against the growth of A431 tumor cell line. The compound 2b containing 3-chloroaniline ring was as potent as PD 153035 against EGFR kinase and showed about 5.4-fold better potency than PD153035 in the inhibition of growth of A431 cell line with good selectivity.

ACCESSION NUMBER: 2002093425 MEDLINE  
DOCUMENT NUMBER: 21680715 PubMed ID: 11822173  
TITLE: 1,4-dioxane-fused 4-anilinoquinazoline as inhibitors of epidermal growth factor receptor kinase.  
AUTHOR: Lee J Y; Park Y K; Seo S H; So I S; Chung H K; Yang B S; Lee S J; Park H; Lee Y S  
CORPORATE SOURCE: Medicinal Chemistry Research Center, Korea Institute of Science & Technology, P.O. Box 131, Cheongryang, Seoul 130-650, Korea.. yslee@kist.re.kr  
SOURCE: ARCHIV DER PHARMAZIE, (2001 Nov) 334 (11) 357-60.  
Journal code: 0330167. ISSN: 0365-6233.  
PUB. COUNTRY: Germany: Germany, Federal Republic of  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200204  
ENTRY DATE: Entered STN: 20020202  
Last Updated on STN: 20020403  
Entered Medline: 20020401

*bad date*

L2 ANSWER 11 OF 143 MEDLINE  
TI Comparison of the biochemical and kinetic properties of the type 1 receptor tyrosine kinase intracellular domains. Demonstration of differential sensitivity to kinase inhibitors.

AB Epidermal growth factor receptor (EGFR), ErbB-2, and ErbB-4 are members of the type 1 receptor tyrosine kinase family. Overexpression of these receptors, especially ErbB-2 and EGFR, has been implicated in multiple forms of cancer. Inhibitors of EGFR tyrosine kinase activity are being evaluated clinically for cancer therapy. The potency and selectivity of these inhibitors may affect the efficacy and toxicity of therapy. Here we describe the expression, purification, and biochemical comparison of EGFR, ErbB-2, and ErbB-4 intracellular domains. Despite their high degree of sequence homology, the three enzymes have significantly different catalytic properties and substrate kinetics. For example, the catalytic activity of ErbB-2 is less stable than that of EGFR. ErbB-2 uses ATP-Mg as a substrate inefficiently compared with EGFR and ErbB-4. The three enzymes have very similar substrate preferences for three optimized peptide substrates, but differences in substrate synergies were observed. We have used the biochemical and kinetic parameters determined from these studies to develop an assay system that accurately measures inhibitor potency and selectivity between the type 1 receptor family. We report that the selectivity profile of molecules in the 4-anilinoquinazoline series can be modified through specific aniline substitutions. Moreover, these compounds have activity in whole cells that reflect the potency and selectivity of target inhibition determined with this assay system.

ACCESSION NUMBER: 2002054098 MEDLINE  
DOCUMENT NUMBER: 21638442 PubMed ID: 11696537  
TITLE: Comparison of the biochemical and kinetic properties of the type 1 receptor tyrosine kinase intracellular domains. Demonstration of differential sensitivity to kinase inhibitors.  
AUTHOR: Brignola Perry S; Lackey Karen; Kadwell Sue H; Hoffman Christine; Horne Earnest; Carter H Luke; Stuart J Darren; Blackburn Kevin; Moyer Mary B; Alligood Krystal J; Knight Wilson B; Wood Edgar R  
CORPORATE SOURCE: Department of Systems Research, GlaxoSmithKline Inc., Research Triangle Park, North Carolina 27709, USA.  
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2002 Jan 11) 277 (2) 1576-85.  
Journal code: 2985121R. ISSN: 0021-9258.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200202  
ENTRY DATE: Entered STN: 20020125  
Last Updated on STN: 20030105  
Entered Medline: 20020207

L2 ANSWER 12 OF 143 MEDLINE

TI Tyrosine kinase inhibitors-ZD1839 (Iressa).

AB Several epithelial tumors display epidermal growth factor receptor (EGFR) overexpression (with or without EGFR gene amplification) that is often associated with increased production of EGFR ligands. This permits the activation of endogenous tumor EGFR via autocrine mechanisms, resulting in cellular proliferation and tumor growth. Interruption of receptor signaling with bivalent EGFR antibodies or with small molecule inhibitors of the EGFR tyrosine kinase results in inhibition of tumor cell proliferation or viability in vitro and in vivo. One small molecule currently undergoing preclinical and clinical investigation is ZD1839 (Iressa), a synthetic anilinoquinazoline capable of inhibiting EGFR tyrosine kinase in vitro. The early results of clinical trials indicate this drug possesses antitumor activity in certain malignancies of the upper aerodigestive tract.

ACCESSION NUMBER: 2001567062 MEDLINE  
DOCUMENT NUMBER: 21526778 PubMed ID: 11673690  
TITLE: Tyrosine kinase inhibitors-ZD1839 (Iressa).

AUTHOR: Arteaga C L; Johnson D H  
 CORPORATE SOURCE: Breast Cancer Program Vanderbilt-Ingram Cancer, Vanderbilt University School of Medicine, 777 Preston Research Building, Nashville, Tennessee 37232-6307, USA.  
 SOURCE: CURRENT OPINION IN ONCOLOGY, (2001 Nov) 13 (6) 491-8. Ref: 34  
 Journal code: 9007265. ISSN: 1040-8746.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 General Review; (REVIEW)  
 (REVIEW, TUTORIAL)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200112  
 ENTRY DATE: Entered STN: 20011024  
 Last Updated on STN: 20020420  
 Entered Medline: 20011226

L2 ANSWER 13 OF 143 MEDLINE

TI The 4-**anilinoquinazoline** class of inhibitors of the erbB family of receptor tyrosine kinases.

AB The erbB family of receptor tyrosine kinase enzymes, and particularly EGFR and HER2/neu, have become important targets for potential anticancer drugs. The substrate protein binding site theoretically is the more attractive intracellular target on these enzymes, possessing lower homology than the ATP site between different receptor kinases. However, a major breakthrough in this field was the discovery that 4-anilinoquinazolines are potent and selective inhibitors, despite binding at the ATP site. The very tight structure-activity relationships shown by these compounds suggested a clearly-defined binding mode, where the quinazoline ring binds in the adenine pocket and the anilino ring binds in an adjacent, unique lipophilic pocket. A unique cysteine (Cys-773) adjacent to the quinazoline binding site has prompted the development of irreversible inhibitors that target this residue. Three 4-**anilinoquinazoline** analogues (two reversible and one irreversible inhibitor) have been evaluated clinically as anticancer drugs. Data from the most advanced, the reversible inhibitor Iressa, suggest that this class of compounds may be of value in cancer chemotherapy.

ACCESSION NUMBER: 2001505477 MEDLINE

DOCUMENT NUMBER: 21245180 PubMed ID: 11347967

TITLE: The 4-**anilinoquinazoline** class of inhibitors of the erbB family of receptor tyrosine kinases.

AUTHOR: Denny W A

CORPORATE SOURCE: Auckland Cancer Society Research Centre, Faculty of Medical and Health Sciences, The University of Auckland, New Zealand.. b.denny@auckland.ac.nz

SOURCE: FARMACO, (2001 Jan-Feb) 56 (1-2) 51-6. Ref: 34  
 Journal code: 8912641. ISSN: 0014-827X.

PUB. COUNTRY: Italy

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 General Review; (REVIEW)  
 (REVIEW, TUTORIAL)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200109

ENTRY DATE: Entered STN: 20010917  
 Last Updated on STN: 20010917  
 Entered Medline: 20010913

L2 ANSWER 14 OF 143 MEDLINE

TI Tyrosine kinase inhibitors. 18. 6-Substituted 4-anilinoquinazolines and 4-anilinopyrido[3,4-d]pyrimidines as soluble, irreversible inhibitors of the epidermal growth factor receptor.

AB 4-**Anilinoquinazoline**- and 4-anilinopyrido[3,4-d]pyrimidine-6-

acrylamides are potent pan-erbB tyrosine kinase inactivators, and one example (CI-1033) is in clinical trial. A series of analogues with a variety of Michael acceptor units at the 6-position were prepared to define the structural requirements for irreversible inhibition. A particular goal was to determine whether additional functions to increase solubility could be appended to the Michael acceptor. Substituted acrylamides were prepared by direct acylation of the corresponding 6-amines with the requisite acid or acid chloride. Vinylsulfonamide derivatives were obtained by acylation of the amines with chloroethylsulfonyl chloride followed by base-promoted elimination. Vinylsulfone and vinylsulfine derivatives were prepared by oxidation and base elimination of a hydroxyethylthio intermediate. The compounds were evaluated for their inhibition of phosphorylation of the isolated EGFR enzyme and for inhibition of EGF-stimulated autophosphorylation of EGFR in A431 cells and of heregulin-stimulated autophosphorylation of erbB2 in MDA-MB 453 cells. Substitution at the nitrogen of the acrylamide was tolerated only with a methyl group; larger substituents were dystherapeutic, and no substitution at all was tolerated at the acrylamide alpha-carbon. In contrast, while electron-donating groups at the acrylamide beta-carbon were not useful, even quite large electron-withdrawing groups (which increase its electrophilicity) were tolerated. A series of derivatives with solubility-enhancing substituents linked to the acrylamide beta-carbon via amides were potent irreversible inhibitors of isolated EGFR (IC50s = 0.4-1.1 nM), with weakly basic morpholine and imidazole derivatives being the best. Vinylsulfonamides were also potent and irreversible inhibitors, but vinylsulfones and vinylsulfines were reversible and only poorly active. Two compounds were evaluated against A431, H125, and MCF-7 xenografts in nude mice but were inferior in these assays to the clinical trial compound CI-1033.

ACCESSION NUMBER: 2001412789 MEDLINE  
DOCUMENT NUMBER: 21355336 PubMed ID: 11462982  
TITLE: Tyrosine kinase inhibitors. 18. 6-Substituted  
4-anilinoquinazolines and 4-anilinopyrido[3,4-d]pyrimidines  
as soluble, irreversible inhibitors of the epidermal growth  
factor receptor.  
AUTHOR: Smaill J B; Showalter H D; Zhou H; Bridges A J; McNamara D  
J; Fry D W; Nelson J M; Sherwood V; Vincent P W; Roberts B  
J; Elliott W L; Denny W A  
CORPORATE SOURCE: Auckland Cancer Society Research Centre, Faculty of  
Medicine and Health Science, The University of Auckland,  
New Zealand.  
SOURCE: JOURNAL OF MEDICINAL CHEMISTRY, (2001 Feb 1) 44 (3) 429-40.  
Journal code: 9716531. ISSN: 0022-2623.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200108  
ENTRY DATE: Entered STN: 20010806  
Last Updated on STN: 20010806  
Entered Medline: 20010802

L2 ANSWER 15 OF 143 MEDLINE  
TI Studies leading to the identification of ZD1839 (IRESSA): an orally  
active, selective epidermal growth factor tyrosine kinase  
inhibitor targeted to the treatment of cancer.  
AB This paper describes the development of the epidermal growth factor  
receptor tyrosine kinase inhibitor ZD1839 from a lead series of 4-  
**anilinoquinazoline** compounds. ZD1839 has suitable properties for  
use as a clinically effective drug and shows activity against human  
tumours. In particular, the use of pharmacokinetic data in the  
development of ZD1839 is discussed.

ACCESSION NUMBER: 2001407954 MEDLINE  
DOCUMENT NUMBER: 21352597 PubMed ID: 11459659

TITLE: Studies leading to the identification of ZD1839 (IRESSA):  
an orally active, selective epidermal growth factor  
receptor tyrosine kinase inhibitor targeted to the  
treatment of cancer.

AUTHOR: Barker A J; Gibson K H; Grundy W; Godfrey A A; Barlow J J;  
Healy M P; Woodburn J R; Ashton S E; Curry B J; Scarlett L;  
Henthorn L; Richards L

CORPORATE SOURCE: AstraZeneca, Cancer and Infection Research, Mereside,  
Alderley Park, Macclesfield, SK10 4TG, Cheshire, UK.

SOURCE: BIOORGANIC AND MEDICINAL CHEMISTRY LETTERS, (2001 Jul 23)  
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Entered Medline: 20010927

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FILE 'MEDLINE, BIOSIS, EMBASE, SCISEARCH, WPIDS, DGENE, JAPIO, FSTA,  
JICST-EPLUS' ENTERED AT 13:48:41 ON 12 MAY 2003

L1 0 S 4-ANILINOQUINAZOLINES  
L2 143 S ANILINOQUINAZOLINE  
L3 1941 S JAK3  
L4 0 S L3 AND L2

=> d ti abs ibib 40-50

L4 HAS NO ANSWERS

'40-50 ' IS NOT A VALID SEARCH STATUS KEYWORD

Search status keywords:

NONE ---- Display only the number of postings.

STATUS -- Display statistics of the search.

ENTER SEARCH STATUS OPTION (NONE), STATUS, OR ?:d l2 ti abs ibib 40-50

'D L20 TI ABS IBIB 40-50' IS NOT A VALID SEARCH STATUS KEYWORD

Search status keywords:

NONE ---- Display only the number of postings.

STATUS -- Display statistics of the search.

ENTER SEARCH STATUS OPTION (NONE), STATUS, OR ?:end

=> d l2 ti abs ibib 40-50

L2 ANSWER 40 OF 143 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

TI 4-anilinoquinazoline derivatives.

AB The invention relates to quinazoline derivatives of formula (I) (wherein:  
R1 represents hydrogen or methoxy; R2 represents methoxy, ethoxy,  
2-methoxyethoxy, 3-methoxypropoxy, 2-ethoxyethoxy, trifluoromethoxy,  
2,2,2-trifluoroethoxy, 2-hydroxyethoxy, 3-hydroxypropoxy,  
2-(N,N-dimethylamino)ethoxy, 3-(N,N-dimethylamino)propoxy,  
2-morpholinoethoxy, 3-morpholinopropoxy, 4-morpholinobutoxy,  
2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy,  
2-(piperazin-1-yl)ethoxy, 3-(piperazin-1-yl)propoxy, 4-(piperazin-1-  
yl)butoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-  
yl)propoxy or 4-(4-methylpiperazin-1-yl)butoxy; the phenyl group bearing  
(R3)2 is selected from: 2-fluoro-5-hydroxyphenyl, 4-bromo-2-fluorophenyl,  
2,4-difluorophenyl, 4-chloro-2-fluorophenyl, 2-fluoro-4-methylphenyl,  
2-fluoro-4-methoxyphenyl, 4-bromo-3-hydroxyphenyl, 4-fluoro-3-  
hydroxyphenyl, 4-chloro-3-hydroxyphenyl, 3-hydroxy-4-methylphenyl,

3-hydroxy-4-methoxyphenyl and 4-cyano-2-fluorophenyl); and salts thereof, processes for their preparation and pharmaceutical compositions containing a compound of formula (I) or a pharmaceutically acceptable salt thereof as active ingredient. The compounds of formula (I) and the pharmaceutically acceptable salts thereof inhibit the effects of VEGF, a property of value in the treatment of a number of disease states including cancer and rheumatoid arthritis ##STR1##

ACCESSION NUMBER: 2001:549746 BIOSIS  
DOCUMENT NUMBER: PREV200100549746  
TITLE: 4-anilinoquinazoline derivatives.  
AUTHOR(S): Thomas, Andrew Peter (1); Johnstone, Craig; Hennequin, Laurent Francois Andre  
CORPORATE SOURCE: (1) Macclesfield UK  
ASSIGNEE: Zeneca Limited, London, UK; Zeneca Pharma S.A., Cergy Cedex, France  
PATENT INFORMATION: US 6291455 September 18, 2001  
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Sep. 18, 2001) Vol. 1250, No. 3, pp. No Pagination. e-file.  
ISSN: 0098-1133.  
DOCUMENT TYPE: Patent  
LANGUAGE: English

L2 ANSWER 41 OF 143 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.  
TI Studies leading to the identification of ZD1839 (Iressa<sup>TM</sup>): An orally active, selective epidermal growth factor receptor tyrosine kinase inhibitor targeted to the treatment of cancer.  
AB This paper describes the development of the epidermal growth factor receptor tyrosine kinase inhibitor ZD1839 from a lead series of 4-anilinoquinazoline compounds. ZD1839 has suitable properties for use as a clinically effective drug and shows activity against human tumours. In particular, the use of pharmacokinetic data in the development of ZD1839 is discussed.

ACCESSION NUMBER: 2001:380840 BIOSIS  
DOCUMENT NUMBER: PREV200100380840  
TITLE: Studies leading to the identification of ZD1839 (Iressa<sup>TM</sup>): An orally active, selective epidermal growth factor receptor tyrosine kinase inhibitor targeted to the treatment of cancer.  
AUTHOR(S): Barker, Andrew J.; Gibson, Keith H. (1); Grundy, Walter; Godfrey, Andrew A.; Barlow, Jeffrey J.; Healy, Mark P.; Woodburn, James R.; Ashton, Susan E.; Curry, Brenda J.; Scarlett, Lynn; Henthorn, Lianne; Richards, Laura  
CORPORATE SOURCE: (1) Cancer and Infection Research, AstraZeneca, Mereside, Alderley Park, Macclesfield, Cheshire, SK10 4TG:  
keith.gibson@astrazeneca.com UK  
SOURCE: Bioorganic & Medicinal Chemistry Letters, (23 July, 2001) Vol. 11, No. 14, pp. 1911-1914. print.  
ISSN: 0960-894X.  
DOCUMENT TYPE: Article  
LANGUAGE: English  
SUMMARY LANGUAGE: English

L2 ANSWER 42 OF 143 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.  
TI Tyrosine kinase inhibitors. 18. 6-substituted 4-anilinoquinazolines and 4-anilinopyrido(3,4-d)pyrimidines as soluble, irreversible inhibitors of the epidermal growth factor receptor.  
AB 4-Anilinoquinazoline- and 4-anilinopyrido(3,4-d)pyrimidine-6-acrylamides are potent pan-erbB tyrosine kinase inactivators, and one example (CI-1033) is in clinical trial. A series of analogues with a variety of Michael acceptor units at the 6-position were prepared to define the structural requirements for irreversible inhibition. A particular goal was to determine whether additional functions to increase solubility could be appended to the Michael acceptor. Substituted

acrylamides were prepared by direct acylation of the corresponding 6-amines with the requisite acid or acid chloride. Vinylsulfonamide derivatives were obtained by acylation of the amines with chloroethylsulfonyl chloride followed by base-promoted elimination. Vinylsulfone and vinylsulfine derivatives were prepared by oxidation and base elimination of a hydroxyethylthio intermediate. The compounds were evaluated for their inhibition of phosphorylation of the isolated EGFR enzyme and for inhibition of EGF-stimulated autophosphorylation of EGFR in A431 cells and of heregulin-stimulated autophosphorylation of erbB2 in MDA-MB 453 cells. Substitution at the nitrogen of the acrylamide was tolerated only with a methyl group; larger substituents were dystherapeutic, and no substitution at all was tolerated at the acrylamide alpha-carbon. In contrast, while electron-donating groups at the acrylamide beta-carbon were not useful, even quite large electron-withdrawing groups (which increase its electrophilicity) were tolerated. A series of derivatives with solubility-enhancing substituents linked to the acrylamide beta-carbon via amides were potent irreversible inhibitors of isolated EGFR (IC50s = 0.4-1.1 nM), with weakly basic morpholine and imidazole derivatives being the best. Vinylsulfonamides were also potent and irreversible inhibitors, but vinylsulfones and vinylsulfines were reversible and only poorly active. Two compounds were evaluated against A431, H125, and MCF-7 xenografts in nude mice but were inferior in these assays to the clinical trial compound CI-1033.

ACCESSION NUMBER: 2001:350452 BIOSIS  
DOCUMENT NUMBER: PREV200100350452  
TITLE: Tyrosine kinase inhibitors. 18. 6-substituted  
4-anilinoquinazolines and 4-anilinopyrido(3,4-d)pyrimidines  
as soluble, irreversible inhibitors of the epidermal growth  
factor receptor.  
AUTHOR(S): Smaill, Jeff B.; Showalter, H. D. Hollis; Zhou, Hairong;  
Bridges, Alexander J.; McNamara, Dennis J.; Fry, David W.;  
Nelson, James M.; Sherwood, Veronika; Vincent, Patrick W.;  
Roberts, Bill J.; Elliott, William L.; Denny, William A.  
(1)  
CORPORATE SOURCE: (1) Auckland Cancer Society Research Centre, Faculty of  
Medicine and Health Science, The University of Auckland,  
Auckland: b.denny@auckland.ac.nz New Zealand  
SOURCE: Journal of Medicinal Chemistry, (February 1, 2001) Vol. 44,  
No. 3, pp. 429-440. print.  
ISSN: 0022-2623.  
DOCUMENT TYPE: Article  
LANGUAGE: English  
SUMMARY LANGUAGE: English

L2 ANSWER 43 OF 143 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.  
TI Structural determinants for potent, selective dual site inhibition of  
human pp60c-src by 4-anilinoquinazolines.  
AB The kinetic mechanisms for the inhibition of pp60c-src tyrosine kinase  
(Src TK) by 4-anilinoquinazolines, an important class of chemicals as  
protein kinase inhibitors, were investigated. 4-Anilinoquinazolines with a  
bulky group at the 4'-position of the anilino group were shown to be  
competitive with both ATP and peptide, whereas molecules lacking such a  
bulky group only displayed an inhibition pattern typical of those  
competitive with ATP and noncompetitive with peptide. Modifications of the  
substituents on the carbocyclic ring did not perturb the inhibition  
pattern although the affinities of these modified inhibitors for Src TK  
were affected. Structural modeling of Src TK with inhibitor and peptide  
substrate bound indicated a direct atomic conflict between the bulky  
4-position group and the hydroxy of the peptide tyrosyl to which the  
gamma-phosphate of ATP is transferred during the kinase reaction. This  
atomic conflict would likely prevent simultaneous binding of both  
inhibitor and peptide, consistent with the observed kinetic  
competitiveness of the inhibitor with peptide. The dual site inhibitors  
appeared to have both enhanced potency and selectivity for Src TK. One

such inhibitor, 4-(4'-phenoxyanilino)-6,7-dimethoxyquinazoline, had a 15 nM potency against Src TK and was selective over receptor tyrosine kinases VEGFR2 by 88-fold and C-fms by 190-fold.

ACCESSION NUMBER: 2001:339436 BIOSIS  
DOCUMENT NUMBER: PREV200100339436  
TITLE: Structural determinants for potent, selective dual site inhibition of human pp60c-src by 4-anilinoquinazolines.  
AUTHOR(S): Tian, Gaochao (1); Cory, Michael; Smith, Albert A.; Knight, W. Blaine  
CORPORATE SOURCE: (1) Department of Lead Discovery, AstraZeneca Pharmaceuticals, 1800 Concord Pike, Wilmington, DE, 19850-5437; gaochao.tian@astrazeneca.com USA  
SOURCE: Biochemistry, (June 19, 2001) Vol. 40, No. 24, pp. 7084-7091. print.  
ISSN: 0006-2960.  
DOCUMENT TYPE: Article  
LANGUAGE: English  
SUMMARY LANGUAGE: English

L2 ANSWER 44 OF 143 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.  
TI DNA interaction of the tyrosine protein kinase inhibitor PD153035 and its N-methyl analogue.  
AB The brominated **anilinoquinazoline** derivative PD153035 exhibits a very high affinity and selectivity for the epidermal growth factor receptor tyrosine kinase (EGF-R TK) and shows a remarkable cytotoxicity against several types of tumor cell lines. In contrast, its N-methyl derivative, designated EBE-A22, has no effect on EGF-R TK but maintains a high cytotoxic profile. The present study was performed to explore the possibility that PD153035 and its N-methyl analogue might interact with double-stranded DNA, which is a primary target for many conventional antitumor agents. We studied the strength and mode of binding to DNA of PD153035 and EBE-A22 by means of absorption, fluorescence, and circular and linear dichroism as well as by a relaxation assay using human DNA topoisomerases. The results of various optical and gel electrophoresis techniques converge to show that both drugs bind to DNA and behave as typical intercalating agents. In particular, EBE-A22 unwinds supercoiled plasmid, stabilizes duplex DNA against heat denaturation, and produces negative CD and ELD signals, as expected for an intercalating agent. Extensive DNase I footprinting experiments performed with a large range of DNA substrates show that EBE-A22, but not PD153035, interacts preferentially with GC-rich sequences and discriminates against homooligomeric runs of A and T which are often cut more readily by the enzyme in the presence of the drug compared to the control. Altogether, the results provide the first experimental evidence that DNA is a target of **anilinoquinazoline** derivatives and suggest that this N-methylated ring system is a valid candidate for the development of DNA-targeted cytotoxic compounds. The possible relevance of selective DNA binding to activity is considered. The unexpected GC-selective binding properties of EBE-A22 entreat further exploration into the use of N-methylanilinoquinazoline derivatives as tools for designing sequence-specific DNA binding ligands.

ACCESSION NUMBER: 2001:283617 BIOSIS  
DOCUMENT NUMBER: PREV200100283617  
TITLE: DNA interaction of the tyrosine protein kinase inhibitor PD153035 and its N-methyl analogue.  
AUTHOR(S): Goossens, Jean-Francois; Bouey-Bencteux, Edith; Houssin, Raymond; Henichart, Jean-Pierre; Colson, Pierre; Houssier, Claude; Laine, William; Baldeyrou, Brigitte; Bailly, Christian (1)  
CORPORATE SOURCE: (1) Laboratoire de Pharmacologie Antitumorale du Centre Oscar Lambret, INSERM U-524, IRCL, Place de Verdun, 59045, Lille: bailly@lille.inserm.fr France  
SOURCE: Biochemistry, (April 17, 2001) Vol. 40, No. 15, pp. 4663-4671. print.



ISSN: 0006-2960.

DOCUMENT TYPE: Article  
LANGUAGE: English  
SUMMARY LANGUAGE: English

L2 ANSWER 45 OF 143 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

TI Biological activity of some 4-anilinoquinazolines: Cytotoxic, genotoxic and antiprotease effects, induction of necrosis and changes of actin cytoskeleton.

AB Fourteen substituted 4-anilinoquinazolines have been tested for cytotoxic effect and structure activity relationships. The most active derivatives were substituted by chlorine or bromine group in the aromatic ring, in the pyrimidine ring by morpholine group and in the aniline skeleton by nitro group in position 4 or 2. Derivatives 6-bromo-2-(morpholin-1-yl)-4-(4'-nitroanilino)quinazoline, 6-bromo-2-morpholin-1-yl)-4-anilinoquinazoline, 2-(morpholin-1-yl)-4-(4'-bromoanilino)-quinazoline and 6-chloro-2-(morpholin-1-yl)-4-(4'-nitroanilino)quinazoline inhibited growth of tumor cell lines HeLa, B16 and L1210. Mutagenic data provided by Ames test showed, that the compounds 6-bromo-2-morpholin-1-yl)-4-anilinoquinazoline and 2-(morpholin-1-yl)-4-(4'-bromoanilino)quinazoline did not exhibit the mutagenic effect, whereas the compounds 6-bromo-2-(morpholin-1-yl)-4-(4'-nitroanilino)quinazoline and 6-chloro-2-(morpholin-1-yl)-4-(4'-nitroanilino)quinazoline increased slightly the number of revertants of the strain TA 98 without metabolic activation. Concentration 26  $\mu\text{mol/L}$  of 6-bromo-2-(morpholin-1-yl)-4-anilinoquinazoline induced necrosis of tumor cells B16. Concentration 5.2  $\mu\text{mol/L}$  induced a significant increase of filamentous actin in the transformed HepG2 cells. Derivatives 6-bromo-2-(morpholin-1-yl)-4-(4'-nitroanilino)quinazoline, 6-bromo-2-morpholin-1-yl)-4-anilinoquinazoline, 2-(morpholin-1-yl)-4-(4'-bromoanilino)quinazoline and 6-chloro-2-(morpholin-1-yl)-4-(4'-nitroanilino)quinazoline exhibited antiprotease effect on plasmin. This results could be relevant for the anticancer properties of these compounds.

ACCESSION NUMBER: 2001:215966 BIOSIS

DOCUMENT NUMBER: PREV200100215966

TITLE: Biological activity of some 4-anilinoquinazolines: Cytotoxic, genotoxic and antiprotease effects, induction of necrosis and changes of actin cytoskeleton.

AUTHOR(S): Jantova, S. (1); Urbancikova, M.; Maliar, T.; Mikulasova, M. (1); Rauko, P.; Cipak, L.; Kubikova, J. (1); Stankovsky, S.; Spirkova, K.

CORPORATE SOURCE: (1) Department of Biochemistry and Microbiology, Faculty of Chemical Technology, Slovak University of Technology, 812 37, Bratislava: jantova@chtf.stuba.sk Slovakia

SOURCE: Neoplasma (Bratislava), (2001) Vol. 48, No. 1, pp. 52-60. print.  
ISSN: 0028-2685.

DOCUMENT TYPE: Article  
LANGUAGE: English  
SUMMARY LANGUAGE: English

L2 ANSWER 46 OF 143 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

TI Design of a chimeric 3-methyl-1,2,3-triazene with mixed receptor tyrosine kinase and DNA damaging properties: A novel tumor targeting strategy.

AB The mixed epidermal growth factor receptor (EGFR)-DNA targeting properties of SMA41, a 6-(3-methyl-1,2,3-triazen-1-yl)-4-anilinoquinazoline designed to release N4-m-tolyl-quinazoline-4,6-diamine henceforth referred to as SMA52 (an inhibitor of EGFR tyrosine kinase (TK)) and methyl diazonium (a DNA methylating species) were studied in the O6-methylguanine-DNA methyltransferase (MGMT)-proficient and high EGFR-expressing epidermoid carcinoma of the vulva cell line A431. The effects of SMA41 were compared with those of SMA52 alone, and temozolomide (TEM), a clinical prodrug of 5-(3-methyltriazene-1-yl)imidazole-4-

carboxamide (MTIC) that is inactive in MGMT-proficient cells. The results showed that 1) the chimeric SMA41 could degrade in serum-containing medium (t<sub>1/2</sub> of approx 30 min) to generate, as predicted, the free inhibitor SMA52 as the most abundant metabolite (approx 81% yield); 2) in contrast to SMA52 alone, the chimeric SMA41 and TEM induced significant DNA damage in A431 cells after 30-min or 2-h drug exposures, as confirmed by alkaline single-cell gel microelectrophoresis (comet) assay; 3) SMA41 showed 5-fold greater affinity for the ATP binding site of EGFR than independently synthesized SMA52 in an enzyme assay and blocked EGF-induced tyrosine phosphorylation and EGFR autophosphorylation in A431 cells in a dose-dependent manner; 4) these mixed targeting properties of SMA41, combined with its ability to be converted to another potent EGFR TK inhibitor (e.g., SMA52) by hydrolytic cleavage, translated into over 8-fold greater antiproliferative activity than TEM, which showed no EGFR targeting properties (IC<sub>50</sub> competitive binding >100 µM); 5) under continuous drug exposure (3-6-day sulforhodamine and clonogenic assays), SMA41 was almost equipotent with SMA52; however, in a short 2-h drug exposure followed by incubation in drug-free media, SMA52 showed an almost complete loss of antiproliferative activity over the whole dose range. In contrast, SMA41 retained almost 100% of its activity, indicating a more sustained growth inhibitory activity. The results in toto suggest that the superior antiproliferative activity of SMA41 may be due to a combination of events associated with its binary EGFR TK and DNA targeting properties.

ACCESSION NUMBER: 2001:181985 BIOSIS  
DOCUMENT NUMBER: PREV200100181985  
TITLE: Design of a chimeric 3-methyl-1,2,3-triazene with mixed receptor tyrosine kinase and DNA damaging properties: A novel tumor targeting strategy.  
AUTHOR(S): Matheson, Stephanie L.; McNamee, James; Jean-Claude, Bertrand J. (1)  
CORPORATE SOURCE: (1) Cancer Drug Research Laboratory, Department of Medicine, Division of Medical Oncology, McGill University Health Center/Royal Victoria Hospital, 687 Pine Ave. West, Room M-719, Montreal, PQ, H3A 1A1: bertrand@med.mcgill.ca Canada  
SOURCE: Journal of Pharmacology and Experimental Therapeutics, (March, 2001) Vol. 296, No. 3, pp. 832-840. print.  
ISSN: 0022-3565.  
DOCUMENT TYPE: Article  
LANGUAGE: English  
SUMMARY LANGUAGE: English

L2 ANSWER 47 OF 143 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.  
TI Inhibitors of Src tyrosine kinase: The preparation and structure: Activity relationship of 4-anilino-3-cyanoquinolines and 4-anilinoquinazolines.  
AB Src is a nonreceptor tyrosine kinase involved in signaling pathways that control proliferation, migration, and angiogenesis. Increased Src expression and activity are associated with an increase in tumor malignancy and poor prognosis. Several quinolines and quinazolines were identified as potent and selective inhibitors of Src kinase activity.

ACCESSION NUMBER: 2000:543113 BIOSIS  
DOCUMENT NUMBER: PREV200000543113  
TITLE: Inhibitors of Src tyrosine kinase: The preparation and structure: Activity relationship of 4-anilino-3-cyanoquinolines and 4-anilinoquinazolines.  
AUTHOR(S): Wang, Yanong D. (1); Miller, Karen; Boschelli, Diane H.; Ye, Fei; Wu, Biqi; Floyd, M. Brawner; Powell, Dennis W.; Wissner, Allan; Weber, Jennifer M.; Boschelli, Frank  
CORPORATE SOURCE: (1) Chemical Sciences and Oncology, Wyeth-Ayerst Research, Pearl River, NY, 10965 USA  
SOURCE: Bioorganic & Medicinal Chemistry Letters, (6 November, 2000) Vol. 10, No. 21, pp. 2477-2480. print.  
ISSN: 0960-894X.  
DOCUMENT TYPE: Article

LANGUAGE: English  
SUMMARY LANGUAGE: English

L2 ANSWER 48 OF 143 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.  
TI 4-Anilino-6,7-dialkoxyquinoline-3-carbonitrile inhibitors of epidermal growth factor receptor kinase and their bioisosteric relationship to the 4-anilino-6,7-dialkoxyquinazoline inhibitors.  
AB The synthesis and SAR of a series of 4-anilino-6,7-dialkoxyquinoline-3-carbonitrile inhibitors of epidermal growth factor receptor (EGF-R) kinase are described. Condensation of 3,4-dialkoxyanilines with ethyl (ethoxymethylene)cyanoacetate followed by thermal cyclization gave, regiospecifically, 6,7-dialkoxy-4-oxo-1,4-dihydroquinoline-3-carbonitriles. Chlorination (POCl<sub>3</sub>) followed by the reaction with substituted anilines furnished the 4-anilino-6,7-dialkoxyquinoline-3-carbonitrile inhibitors of EGF-R kinase. An alternate synthesis of these compounds starts with a methyl 3,4-dialkoxybenzoate. Nitration followed by reduction (Fe, NH<sub>4</sub>Cl, MeOH-H<sub>2</sub>O) gave a methyl 2-amino-4,5-dialkoxybenzoate. Amidine formation using DMF-acetal followed by cyclization using LiCH<sub>2</sub>CN furnished a 6,7-dialkoxy-4-oxo-1,4-dihydroquinoline-3-carbonitrile, which was transformed as before. Compounds containing acid, ester, amide, carbinol, and aldehyde groups at the 3-position of the quinoline ring were also prepared for comparison, as were several 1-anilino-6,7-dimethoxyisoquinoline-4-carbonitriles. The compounds were evaluated for their ability to inhibit the autophosphorylation of the catalytic domain of EGF-R. The SAR of these inhibitors with respect to the nature of the 6,7-alkoxy groups, the aniline substituents, and the substituent at the 3-position was studied. The compounds were further evaluated for their ability to inhibit the growth of cell lines that overexpress EGF-R or HER-2. It was found that 4-anilinoquinoline-3-carbonitriles are effective inhibitors of EGF-R kinase with activity comparable to the 4-anilinoquinazoline-based inhibitors. A new homology model of EGF-R kinase was constructed based on the X-ray structures of Hck and FGF receptor-1 kinase. The model suggests that with the quinazoline-based inhibitors, the N3 atom is hydrogen-bonded to a water molecule which, in turn, interacts with Thr 830. It is proposed that the quinoline-3-carbonitriles bind in a similar manner where the water molecule is displaced by the cyano group which interacts with the same Thr residue.

ACCESSION NUMBER: 2000:438632 BIOSIS  
DOCUMENT NUMBER: PREV200000438632  
TITLE: 4-Anilino-6,7-dialkoxyquinoline-3-carbonitrile inhibitors of epidermal growth factor receptor kinase and their bioisosteric relationship to the 4-anilino-6,7-dialkoxyquinazoline inhibitors.  
AUTHOR(S): Wissner, Allan (1); Berger, Dan M.; Boschelli, Diane H.; Floyd, M. Brawner, Jr.; Greenberger, Lee M.; Gruber, Brian C.; Johnson, Bernard D.; Mamuya, Nellie; Nilakantan, Ramaswamy; Reich, Marvin F.; Shen, Ru; Tsou, Hwei-Ru; Upeslakis, Erik; Wang, Yu Fen; Wu, Biqi; Ye, Fei; Zhang, Nan  
CORPORATE SOURCE: (1) Division of American Home Products, Wyeth-Ayerst Research, 401 North Middletown Road, Pearl River, NY, 10965-1215 USA  
SOURCE: Journal of Medicinal Chemistry, (August 24, 2000) Vol. 43, No. 17, pp. 3244-3256. print.  
ISSN: 0022-2623.  
DOCUMENT TYPE: Article  
LANGUAGE: English  
SUMMARY LANGUAGE: English

L2 ANSWER 49 OF 143 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.  
TI Structure-based design of potent inhibitors of EGF-receptor tyrosine kinase as anti-cancer agents.  
AB In a systematic effort to design inhibitors of the epidermal growth factor

receptor (EGFR) family protein tyrosine kinases (PTK) as anti-cancer agents, we have constructed a three-dimensional homology model of the EGFR kinase domain and used molecular modeling methods for the structure-based design of analogs of the active metabolite of leflunomide (LFM) with potent and specific inhibitory activity against EGFR. These docking studies identified alpha-cyano-beta-hydroxy-beta-methyl-N-(4-(trifluoromethoxy)phenyl)-propenamide (LFM-A12) as our lead compound, which was predicted to bind to the EGFR catalytic site in a planar conformation. LFM-A12 inhibited the proliferation ( $IC_{50} = 26.3 \mu M$ ) and in vitro invasiveness ( $IC_{50} = 28.4 \mu M$ ) of EGFR positive human breast cancer cells in a concentration-dependent fashion. Similarly, the model of the EGFR binding pocket was used in combination with docking procedures to predict the favorable placement of chemical groups with defined sizes at multiple modification sites on another class of EGFR inhibitors, the 4-anilinoquinazoline. This approach has led to the successful design of a dibromo quinazoline derivative, WHI-P97, which had an estimated  $K_i$  value of  $0.09 \mu M$  from modeling studies and a measured  $IC_{50}$  value of  $2.5 \mu M$  in EGFR kinase inhibition assays. WHI-P97 effectively inhibited the in vitro invasiveness of EGFR-positive human cancer cells in a concentration-dependent manner. However, unlike LFM-A12, the quinazoline compounds are not specific for EGFR.

ACCESSION NUMBER: 2000:231779 BIOSIS  
DOCUMENT NUMBER: PREV200000231779  
TITLE: Structure-based design of potent inhibitors of EGF-receptor tyrosine kinase as anti-cancer agents.  
AUTHOR(S): Ghosh, Sutapa; Narla, Rama Krishna; Zheng, Yaguo; Liu, Xing-Ping; Jun, Xiao; Mao, Chen; Sudbeck, Elise A.; Uckun, Fatih M. (1)  
CORPORATE SOURCE: (1) Parker Hughes Institute, 2665 Long Lake Road, Suite 330, St Paul, MN, 55113 USA  
SOURCE: Anti-Cancer Drug Design, (Oct., 1999) Vol. 14, No. 5, pp. 403-410.  
ISSN: 0266-9536.  
DOCUMENT TYPE: Article  
LANGUAGE: English  
SUMMARY LANGUAGE: English

L2 ANSWER 50 OF 143 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.  
TI Tyrosine kinase inhibitors. 17. Irreversible inhibitors of the epidermal growth factor receptor: 4-(Phenylamino)quinazoline- and 4-(phenylamino)pyrido(3,2-d)pyrimidine-6-acrylamides bearing additional solubilizing functions.  
AB 4-Anilinoquinazoline- and 4-anilinopyrido(3,2-d)pyrimidine-6-acrylamides substituted with solubilizing 7-alkylamine or 7-alkoxyamine side chains were prepared by reaction of the corresponding 6-amines with acrylic acid or acrylic acid anhydrides. In the pyrido(3,2-d)-pyrimidine series, the intermediate 6-amino-7-alkylamines were prepared from 7-bromo-6-fluoropyrido(3,2-d)pyrimidine via Stille coupling with the appropriate stannane under palladium-(0) catalysis. This proved a versatile method for the introduction of cationic solubilizing side chains. The compounds were evaluated for their inhibition of phosphorylation of the isolated EGFR enzyme and for inhibition of EGF-stimulated autophosphorylation of EGFR in A431 cells and of heregulin-stimulated autophosphorylation of erbB2 in MDA-MB 453 cells. Quinazoline analogues with 7-alkoxyamine solubilizing groups were potent irreversible inhibitors of the isolated EGFR enzyme, with  $IC_{50}$ (app) values from 2 to 4 nM, and potently inhibited both EGFR and erbB2 autophosphorylation in cells. 7-Alkylamino- and 7-alkoxyaminopyrido(3,2-d)pyrimidines were also irreversible inhibitors with equal or superior potency against the isolated enzyme but were less effective in the cellular autophosphorylation assays. Both quinazoline- and pyrido(3,2-d)pyrimidine-6-acrylamides bound at the ATP site alkylating cysteine 773, as shown by electrospray ionization mass spectrometry, and had similar rates of absorptive and secretory transport in Caco-2 cells. A

comparison of two 7-propoxymorpholide analogues showed that the pyrido(3,2-d)pyrimidine-6-acrylamide had greater amide instability and higher acrylamide reactivity, being converted to glutathione adducts in cells more rapidly than the corresponding quinazoline. This difference may contribute to the observed lower cellular potency of the pyrido(3,2-d)pyrimidine-6-acrylamides. Selected compounds showed high in vivo activity against A431 xenografts on oral dosing, with the quinazolines being superior to the pyrido(3,2-d)pyrimidines. Overall, the quinazolines proved superior to previous analogues in terms of aqueous solubility, potency, and in vivo antitumor activity, and one example (CI 1033) has been selected for clinical evaluation.

ACCESSION NUMBER: 2000:198462 BIOSIS

DOCUMENT NUMBER: PREV200000198462

TITLE: Tyrosine kinase inhibitors. 17. Irreversible inhibitors of the epidermal growth factor receptor: 4-(Phenylamino)quinazoline- and 4-(phenylamino)pyrido(3,2-d)pyrimidine-6-acrylamides bearing additional solubilizing functions.

AUTHOR(S): Smaill, Jeff B.; Rewcastle, Gordon W.; Loo, Joseph A.; Greis, Kenneth D.; Chan, O. Helen; Reyner, Eric L.; Lipka, Elke; Showalter, H. D. Hollis; Vincent, Patrick W.; Elliott, William L.; Denny, William A. (1)

CORPORATE SOURCE: (1) Faculty of Medical and Health Sciences, Auckland Cancer Society Research Centre, University of Auckland, Auckland New Zealand

SOURCE: Journal of Medicinal Chemistry, (April 6, 2000) Vol. 43, No. 7, pp. 1380-1397.  
ISSN: 0022-2623.

DOCUMENT TYPE: Article

LANGUAGE: English

SUMMARY LANGUAGE: English

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NEWS 28 Mar 20 EVENTLINE will be removed from STN  
NEWS 29 Mar 24 PATDPAFULL now available on STN  
NEWS 30 Mar 24 Additional information for trade-named substances without  
structures available in REGISTRY  
NEWS 31 Apr 11 Display formats in DGENE enhanced  
NEWS 32 Apr 14 MEDLINE Reload  
NEWS 33 Apr 17 Polymer searching in REGISTRY enhanced  
NEWS 34 Apr 21 Indexing from 1947 to 1956 being added to records in CA/CAPLUS  
NEWS 35 Apr 21 New current-awareness alert (SDI) frequency in  
WPIDS/WPINDEX/WPIX  
NEWS 36 Apr 28 RDISCLOSURE now available on STN  
NEWS 37 May 05 Pharmacokinetic information and systematic chemical names  
added to PHAR

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AND CURRENT DISCOVER FILE IS DATED 01 APRIL 2003  
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=> s mapk  
L1 15104 MAPK

=> s janex-1  
L2 5 JANEX-1

=> d l2 ti abs ibib tot

L2 ANSWER 1 OF 5 MEDLINE

TI Targeting JAK3 with JANEX-1 for prevention of autoimmune type 1 diabetes in NOD mice.

AB Here we show that Janus kinase (JAK) 3 is an important molecular target for treatment of autoimmune insulin-dependent (type 1) diabetes mellitus. The rationally designed JAK3 inhibitor JANEX-1 exhibited potent immunomodulatory activity and delayed the onset of diabetes in the NOD mouse model of autoimmune type 1 diabetes. Whereas 60% of vehicle-treated control NOD mice became diabetic by 25 weeks, the incidence of diabetes at 25 weeks was only 9% for NOD females treated with daily injections of JANEX-1 (100 mg/kg/day) from Week 10 through Week 25 (P = 0.007). Furthermore, JANEX-1 prevented the development of insulinitis and diabetes in NOD-scid/scid females after adoptive transfer of splenocytes from diabetic NOD females. Chemical inhibitors such as JANEX-1 may provide the basis for effective treatment modalities against human type 1 diabetes. To our knowledge, this is the first report of the immunosuppressive activity of a JAK3 inhibitor in the context of an autoimmune disease.

ACCESSION NUMBER: 2003187830 IN-PROCESS

DOCUMENT NUMBER: 22592724 PubMed ID: 12706408

TITLE: Targeting JAK3 with JANEX-1 for prevention of autoimmune type 1 diabetes in NOD mice.

AUTHOR: Cetkovic-Cvrlje Marina; Dragt Angela L; Vassilev Alexei; Liu Xing Ping; Uckun Fatih M

CORPORATE SOURCE: Department of Immunology, Parker Hughes Institute, 2699 Patton Road, St. Paul, 55113, MN, USA.

SOURCE: CLINICAL IMMUNOLOGY, (2003 Mar) 106 (3) 213-25.  
Journal code: 100883537. ISSN: 1521-6616.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals  
ENTRY DATE: Entered STN: 20030423  
Last Updated on STN: 20030423

L2 ANSWER 2 OF 5 MEDLINE

TI Janus kinase 3 inhibitor WHI-P131/**JANEX-1** prevents  
graft-versus-host disease but spares the graft-versus-leukemia function of  
the bone marrow allografts in a murine bone marrow transplantation model.  
AB The purpose of the present study was to evaluate the effects of  
graft-versus-host disease (GVHD) prophylaxis with the Janus kinase 3  
(JAK3) inhibitor WHI-P131/**JANEX-1** on the  
graft-versus-leukemic (GVL) function of marrow allografts in mice  
undergoing bone marrow transplantation (BMT) after being challenged with  
an otherwise invariably fatal dose of BCL-1 leukemia cells. GVHD  
prophylaxis using WHI-P131 markedly improved the survival outcome after  
BMT. The probability of survival at 30 days after BMT was 11% +/- 6% for  
vehicle-treated recipients (median survival time, 25 days) versus 63% +/-  
12% for recipients treated with WHI-P131 (median survival time, 36 days; P  
<.0001). Because WHI-P131 is devoid of antileukemic activity against  
BCL-1 leukemia cells, this marked improvement in survival outcome was due  
to reduced incidence of GVHD-associated fatalities combined with sustained  
GVL function of the allografts in the WHI-P131 group. Notably, adoptive  
transfer experiments demonstrated that the spleens of WHI-P131-treated  
allograft recipients contained less than 0.001% BCL-1 cells. Notably,  
GVHD prophylaxis with WHI-P131 plus methotrexate resulted in 100% survival  
of mice receiving allotransplants challenged with an otherwise invariably  
fatal dose of BCL-1 leukemia. Taken together, our results provide strong  
experimental evidence that GVHD prophylaxis using WHI-P131 does not impair  
the GVL function of the allografts and consequently contributes to an  
improved post-BMT survival outcome of the recipient mice.

ACCESSION NUMBER: 2002271117 MEDLINE  
DOCUMENT NUMBER: 22005998 PubMed ID: 12010825  
TITLE: Janus kinase 3 inhibitor WHI-P131/**JANEX-1**  
prevents graft-versus-host disease but spares the  
graft-versus-leukemia function of the bone marrow  
allografts in a murine bone marrow transplantation model.  
AUTHOR: Uckun Fatih M; Roers Bertram A; Waurzyniak Barbara; Liu  
Xing-Ping; Cetkovic-Cvrlje Marina  
CORPORATE SOURCE: Experimental BMT Program, Parker Hughes Cancer Center and  
Department of Immunology, Parker Hughes Institute, St Paul,  
MN 55113, USA.. faith\_uckun@ih.org  
SOURCE: BLOOD, (2002 Jun 1) 99 (11) 4192-9.  
Journal code: 7603509. ISSN: 0006-4971.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals  
ENTRY MONTH: 200207  
ENTRY DATE: Entered STN: 20020516  
Last Updated on STN: 20020702  
Entered Medline: 20020701

L2 ANSWER 3 OF 5 MEDLINE

TI CYP1A-mediated metabolism of the Janus kinase-3 inhibitor  
4-(4'-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline: structural basis for  
inactivation by regioselective O-demethylation.  
AB Here we report the phase I metabolism of the rationally designed Janus  
kinase-3 (JAK) inhibitor 4-(4'-hydroxyphenyl)-amino-6,7-  
dimethoxyquinazoline (WHI-P131; **JANEX-1**).



**JANEX-1** was metabolized by the cytochrome P450 enzymes CYP1A1 and CYP1A2 in a regioselective fashion to form the biologically inactive 7-O-demethylation product 4-(4'-hydroxyphenyl)-amino-6-methoxy-7-hydroxyquinazoline (**JANEX-1-M**). Our molecular modeling studies indicated that the CYP1A family enzymes bind and demethylate **JANEX-1** at the C-7 position of the quinazoline ring since the alternative binding conformation with demethylation at the C-6 position would result in a severe steric clash with the binding site residues. The metabolism of **JANEX-1** to **JANEX-1-M** in pooled human liver microsomes followed Michaelis-Menten kinetics with V(max) and K(m) values (mean +/- S.D.) of 34.6 +/- 9.8 pmol/min/mg and 107.3 +/- 66.3 microm, respectively. alpha-Naphthoflavone and furafylline, which both inhibit CYP1A2, significantly inhibited the formation of **JANEX-1-M** in human liver microsomes. There was a direct correlation between CYP1A activities and the magnitude of **JANEX-1-M** formation in the liver microsomes from different animal species. A significantly increased metabolic rate for **JANEX-1** was observed in Aroclor 1254-, beta-naphthoflavone-, and 3-methylcholanthrene-induced microsomes but not in clofibrate-, dexamethasone-, isoniazid-, and phenobarbital-induced microsomes. The formation of **JANEX-1-M** in the presence of baculovirus-expressed CYP1A1 and 1A2 was consistent with Michaelis-Menten kinetics. The systemic clearance of **JANEX-1-M** was much faster than that of **JANEX-1** (5525.1 +/- 1926.2 ml/h/kg versus 1458.0 +/- 258.6 ml/h/kg). Consequently, the area under the curve value for **JANEX-1-M** was much smaller than that for **JANEX-1** (27.5 +/- 8.0 versus 94.8 +/- 18.4 microm. h; P < 0.001).

ACCESSION NUMBER: 2002046792 MEDLINE  
DOCUMENT NUMBER: 21610538 PubMed ID: 11744615  
TITLE: CYP1A-mediated metabolism of the Janus kinase-3 inhibitor 4-(4'-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline: structural basis for inactivation by regioselective O-demethylation.  
AUTHOR: Uckun Fatih M; Thoen Jason; Chen Hao; Sudbeck Elise; Mao Chen; Malaviya Ravi; Liu Xing-Ping; Chen Chun-Lin  
CORPORATE SOURCE: Department of Pharmaceutical Sciences, Parker Hughes Cancer Center, 2665 Long Lake Road, Suite 330, St. Paul, MN 55113, USA.. fatih\_uckun@ih.org  
SOURCE: DRUG METABOLISM AND DISPOSITION, (2002 Jan) 30 (1) 74-85. Journal code: 9421550. ISSN: 0090-9556.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200202  
ENTRY DATE: Entered STN: 20020125  
Last Updated on STN: 20020207  
Entered Medline: 20020206

L2 ANSWER 4 OF 5 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.  
TI Janus kinase 3 inhibitor WHI-P131/**JANEX-1** prevents graft-versus-host disease but spares the graft-versus-leukemia function of the bone marrow allografts in a murine bone marrow transplantation model.  
AB The purpose of the present study was to evaluate the effects of graft-versus-host disease (GVHD) prophylaxis with the Janus kinase 3 (JAK3) inhibitor WHI-P131/**JANEX-1** on the graft-versus-leukemic (GVL) function of marrow allografts in mice undergoing bone marrow transplantation (BMT) after being challenged with an otherwise invariably fatal dose of BCL-1 leukemia cells. GVHD prophylaxis using WHI-P131 markedly improved the survival outcome after BMT. The probability of survival at 30 days after BMT was 11% +/- 6% for vehicle-treated recipients (median survival time, 25 days) versus 63% +/- 12% for recipients treated with WHI-P131 (median survival time, 36 days; P

< .0001). Because WHI-P131 is devoid of antileukemic activity against BCL-1 leukemia cells, this marked improvement in survival outcome was due to reduced incidence of GVHD-associated fatalities combined with sustained GVL function of the allografts in the WHI-P131 group. Notably, adoptive transfer experiments demonstrated that the spleens of WHI-P131-treated allograft recipients contained less than 0.001% BCL-1 cells. Notably, GVHD prophylaxis with WHI-P131 plus methotrexate resulted in 100% survival of mice receiving allotransplants challenged with an otherwise invariably fatal dose of BCL-1 leukemia. Taken together, our results provide strong experimental evidence that GVHD prophylaxis using WHI-P131 does not impair the GVL function of the allografts and consequently contributes to an improved post-BMT survival outcome of the recipient mice.

ACCESSION NUMBER: 2002:341660 BIOSIS  
DOCUMENT NUMBER: PREV200200341660  
TITLE: Janus kinase 3 inhibitor WHI-P131/**JANEX-1**  
prevents graft-versus-host disease but spares the  
graft-versus-leukemia function of the bone marrow  
allografts in a murine bone marrow transplantation model.  
AUTHOR(S): Uckun, Fatih M. (1); Roers, Bertram A.; Waurzyniak,  
Barbara; Liu, Xing-Ping; Cetkovic-Cvrlje, Marina  
CORPORATE SOURCE: (1) Parker Hughes Cancer Center, 2665 Long Lake Rd, Suite  
300, St Paul, MN, 55113: fatih\_uckun@ih.org USA  
SOURCE: Blood, (June 1, 2002) Vol. 99, No. 11, pp. 4192-4199.  
<http://www.bloodjournal.org/>. print.  
ISSN: 0006-4971.  
DOCUMENT TYPE: Article  
LANGUAGE: English

L2 ANSWER 5 OF 5 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.  
TI CYP1A-mediated metabolism of the Janus kinase-3 inhibitor  
4-(4'-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline: Structural basis for  
inactivation by regioselective O-demethylation.  
AB Here we report the phase I metabolism of the rationally designed Janus  
kinase-3 (JAK) inhibitor 4-(4'-hydroxyphenyl)-amino-6,7-  
dimethoxyquinazoline (WHI-P131; **JANEX-1**).  
**JANEX-1** was metabolized by the cytochrome P450 enzymes  
CYP1A1 and CYP1A2 in a regioselective fashion to form the biologically  
inactive 7-O-demethylation product 4-(4'-hydroxyphenyl)-amino-6-methoxy-7-  
hydroxyquinazoline (**JANEX-1-M**). Our molecular modeling  
studies indicated that the CYP1A family enzymes bind and demethylate  
**JANEX-1** at the C-7 position of the quinazoline ring  
since the alternative binding conformation with demethylation at the C-6  
position would result in a severe steric clash with the binding site  
residues. The metabolism of **JANEX-1** to **JANEX**  
**-1-M** in pooled human liver microsomes followed Michaelis-Menten  
kinetics with Vmax and Km values (mean +- S.D.) of 34.6 +- 9.8 pmol/min/mg  
and 107.3 +- 66.3 µM, respectively. alpha-Naphthoflavone and furafylline,  
which both inhibit CYP1A2, significantly inhibited the formation of  
**JANEX-1-M** in human liver microsomes. There was a direct  
correlation between CYP1A activities and the magnitude of **JANEX**-  
**1-M** formation in the liver microsomes from different animal  
species. A significantly increased metabolic rate for **JANEX**-  
**1** was observed in Aroclor 1254-, beta-naphthoflavone-, and  
3-methylcholanthrene-induced microsomes but not in clofibrate-,  
dexamethasone-, isoniazid-, and phenobarbital-induced microsomes. The  
formation of **JANEX-1-M** in the presence of  
baculovirus-expressed CYP1A1 and 1A2 was consistent with Michaelis-Menten  
kinetics. The systemic clearance of **JANEX-1-M** was much  
faster than that of **JANEX-1** (5525.1 +- 1926.2 ml/h/kg  
versus 1458.0 +- 258.6 ml/h/kg). Consequently, the area under the curve  
value for **JANEX-1-M** was much smaller than that for  
**JANEX-1** (27.5 +- 8.0 versus 94.8 +- 18.4 µM cntdot h; P  
< 0.001).

ACCESSION NUMBER: 2002:101322 BIOSIS

DOCUMENT NUMBER: PREV200200101322  
TITLE: CYP1A-mediated metabolism of the Janus kinase-3 inhibitor  
4-(4'-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline:  
Structural basis for inactivation by regioselective  
O-demethylation.  
AUTHOR(S): Uckun, Fatih M. (1); Thoen, Jason; Chen, Hao; Sudbeck,  
Elise; Mao, Chen; Malaviya, Ravi; Liu, Xing-Ping; Chen,  
Chun-Lin  
CORPORATE SOURCE: (1) Parker Hughes Cancer Center, 2665 Long Lake Road, Suite  
330, St Paul, MN, 55113: fatih\_uckun@ih.org USA  
SOURCE: Drug Metabolism and Disposition, (January, 2002) Vol. 30,  
No. 1, pp. 74-85. print.  
ISSN: 0090-9556.  
DOCUMENT TYPE: Article  
LANGUAGE: English

=> d his

(FILE 'HOME' ENTERED AT 12:57:26 ON 08 MAY 2003)

FILE 'MEDLINE, BIOSIS' ENTERED AT 12:59:14 ON 08 MAY 2003

L1 15104 S MAPK  
L2 5 S JANEX-1

=> s inhibit () c-jun  
L3 21 INHIBIT (W) C-JUN

=> d l3 ti abs ibib tot

L3 ANSWER 1 OF 21 MEDLINE  
TI Analysis of the NF-kappa B and PI 3-kinase/Akt survival pathways in nerve  
growth factor-dependent neurons.  
AB Nerve growth factor (NGF) readdition to NGF-deprived neurons can halt Jun  
N-terminal kinase (JNK) activation, cytochrome c release, and cell death  
through mechanisms that may involve phosphatidylinositol (PI) 3-kinase,  
Akt, and nuclear factor kappa B (NF-kappaB). We found that expression of  
the NF-kappaB protein c-Rel in NGF-deprived neurons blocks cytochrome c  
release but does not inhibit c-Jun  
phosphorylation. Conversely, inhibition of NF-kappaB in NGF-maintained  
neurons promotes cytochrome c release and cell death. In contrast to  
c-Rel, activated PI 3-kinase and Akt inhibit c-  
Jun phosphorylation but have only a small effect on cytochrome c  
release. Finally, although c-Rel can protect neurons from death caused by  
inhibitors of PI 3-kinase or Akt, NF-kappaB function is not critical for  
Akt-promoted survival. These results suggest that the PI 3-kinase/Akt and  
NF-kappaB survival pathways target distinct cell death events in neurons.  
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ACCESSION NUMBER: 2001544810 MEDLINE  
DOCUMENT NUMBER: 21475972 PubMed ID: 11591132  
TITLE: Analysis of the NF-kappa B and PI 3-kinase/Akt survival  
pathways in nerve growth factor-dependent neurons.  
AUTHOR: Sarmiere P D; Freeman R S  
CORPORATE SOURCE: Department of Pharmacology and Physiology, University of  
Rochester School of Medicine, Rochester, New York 14642,  
USA.  
CONTRACT NUMBER: ES07026 (NIEHS)  
NS34400 (NINDS)  
SOURCE: MOLECULAR AND CELLULAR NEUROSCIENCES, (2001 Sep) 18 (3)  
320-31.  
Journal code: 9100095. ISSN: 1044-7431.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English

FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200112  
ENTRY DATE: Entered STN: 20011010  
Last Updated on STN: 20020919  
Entered Medline: 20011227

L3 ANSWER 2 OF 21 MEDLINE

TI Inhibition of JNK by overexpression of the JNL binding domain of JIP-1 prevents apoptosis in sympathetic neurons.

AB Studies in non-neuronal cells show that c-Jun N-terminal kinases (JNK) play a key role in apoptotic cell death. In some neurons JNK is also thought to initiate cell death by the activation of c-Jun. JNK inhibition has been achieved pharmacologically by inhibiting upstream kinases, but there has been no direct demonstration that inhibition of JNK can prevent neuronal death. We have therefore examined whether the JNK binding domain (JBD) of JNK-interacting protein-1 (JIP-1, a scaffold protein and specific inhibitor of JNK) can inhibit c-Jun phosphorylation and support the survival of sympathetic neurons deprived of NGF. We show that expression of the JBD in >80% of neurons was sufficient to prevent the phosphorylation of c-Jun and its nuclear accumulation as well as abrogate neuronal cell death induced by NGF deprivation. JBD expression also preserved the capacity of mitochondria to reduce MTT. Interestingly, although the PTB domain of JIP was reported to interact with rhoGEF, expression of the JBD domain was sufficient to localize the protein to the membrane cortex and growth cones. Hence, JNK activation is a key event in apoptotic death induced by NGF withdrawal, where its point of action lies upstream of mitochondrial dysfunction.

ACCESSION NUMBER: 2001293128 MEDLINE

DOCUMENT NUMBER: 21264960 PubMed ID: 11121395

TITLE: Inhibition of JNK by overexpression of the JNL binding domain of JIP-1 prevents apoptosis in sympathetic neurons.

AUTHOR: Harding T C; Xue L; Bienemann A; Haywood D; Dickens M; Tolkovsky A M; Uney J B

CORPORATE SOURCE: University Research Centre for Neuroendocrinology and MRC Centre for Synaptic Plasticity, University of Bristol, Marlborough Street, Bristol, BS2 8HW, UK.

SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2001 Feb 16) 276 (7) 4531-4.

Journal code: 2985121R. ISSN: 0021-9258.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200106

ENTRY DATE: Entered STN: 20010702

Last Updated on STN: 20030105

Entered Medline: 20010628

L3 ANSWER 3 OF 21 MEDLINE

TI Insulin-like growth factor-I and Bcl-X(L) inhibit c-jun N-terminal kinase activation and rescue Schwann cells from apoptosis.

AB We previously reported that Schwann cells undergo apoptosis after serum withdrawal. Insulin-like growth factor-I, via phosphatidylinositol-3 kinase, inhibits caspase activation and rescues Schwann cells from serum withdrawal-induced apoptosis. In this study, we examined the role of c-jun N-terminal protein kinase (JNK) in Schwann cell apoptosis induced by serum withdrawal. Activation of both JNK1 and JNK2 was detected 1 h after serum withdrawal with the maximal level detected at 2 h. A dominant negative JNK mutant, JNK (APF), blocked JNK activation induced by serum withdrawal and Schwann cell apoptosis, suggesting JNK activation participates in Schwann cell apoptosis. Serum withdrawal-induced JNK activity was caspase dependent and inhibited by a caspase 3 inhibitor, Ac-DEVD-CHO. Because insulin-like growth factor-I and Bcl-X(L) are both

Schwann cell survival factors, we tested their effects on JNK activation during apoptosis. Insulin-like growth factor-I treatment decreased both JNK1 and JNK2 activity induced by serum withdrawal. LY294002, a phosphatidylinositol-3 kinase inhibitor, blocked insulin-like growth factor-I inhibition on JNK activation, suggesting that phosphatidylinositol-3 kinase mediates the effects of insulin-like growth factor-I. Overexpression of Bcl-X(L) also resulted in less Schwann cell death and inhibition of JNK activation after serum withdrawal. Collectively, these results suggest JNK activation is involved in Schwann cell apoptosis induced by serum withdrawal. Insulin-like growth factor-I and Bcl family proteins rescue Schwann cells, at least in part, by inhibition of JNK activity.

ACCESSION NUMBER: 2001149199 MEDLINE  
DOCUMENT NUMBER: 21103893 PubMed ID: 11158266  
TITLE: Insulin-like growth factor-I and Bcl-X(L) inhibit  
c-jun N-terminal kinase activation and  
rescue Schwann cells from apoptosis.  
AUTHOR: Cheng H L; Steinway M L; Xin X; Feldman E L  
CORPORATE SOURCE: Department of Neurology, University of Michigan, Ann Arbor,  
Michigan, USA.  
CONTRACT NUMBER: NS36778 (NINDS)  
NS38849 (NINDS)  
SOURCE: JOURNAL OF NEUROCHEMISTRY, (2001 Feb) 76 (3) 935-43.  
Journal code: 2985190R. ISSN: 0022-3042.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200103  
ENTRY DATE: Entered STN: 20010404  
Last Updated on STN: 20010404  
Entered Medline: 20010315

L3 ANSWER 4 OF 21 MEDLINE

TI Functional interplay between nuclear factor-kappaB and c-Jun integrated by coactivator p300 determines the survival of nerve growth factor-dependent PC12 cells.

AB Nerve growth factor (NGF) activates the transcription factors nuclear factor kappaB (NF-kappaB) and activator protein-1 (AP-1) in sympathetic neurons. Whereas NGF-inducible NF-kappaB is required for the survival of neurons, c-Jun has the ability to promote neuronal death. In this report, we have examined the effect of NGF withdrawal on c-Jun and NF-kappaB transcription factors in PC12 cells differentiated to a neuronal phenotype. We show that the withdrawal of NGF from these cultures results in de novo synthesis of c-Jun, increase in AP-1 activity, and down-regulation of NF-kappaB activity. To investigate how the signal transduction pathways activating c-Jun and NF-kappaB are differentially regulated by NGF, we performed transcriptional analyses. Expression of RelA (NF-kappaB) suppressed the c-Jun-dependent transcription of c-jun, and this effect was reversed by overexpression of the coactivator p300. RelA's effects on c-Jun transcription were mediated by competitive binding of the carboxy-terminal region of RelA to the CH1 domain of p300, which also binds to c-Jun; deletion of this region abrogated the ability of RelA to inhibit c-Jun activity. Furthermore, the inhibition of endogenous NF-kappaB in NGF-maintained neuronal PC12 cells led to the induction of c-Jun synthesis and a marked increase in cell death. Together, these studies demonstrate a functional interaction between NF-kappaB and c-Jun and suggest a novel mechanism of NF-kappaB-mediated neuroprotection.

ACCESSION NUMBER: 2000110423 MEDLINE  
DOCUMENT NUMBER: 20110423 PubMed ID: 10646503  
TITLE: Functional interplay between nuclear factor-kappaB and  
c-Jun integrated by coactivator p300 determines the  
survival of nerve growth factor-dependent PC12 cells.

AUTHOR: Maggirwar S B; Ramirez S; Tong N; Gelbard H A; Dewhurst S  
CORPORATE SOURCE: Department of Microbiology and Immunology, University of  
Rochester Medical Center, New York 14642, USA..  
sanjay\_maggirwar@urmc.rochester.edu  
CONTRACT NUMBER: PO1 MH57556 (NIMH)  
SOURCE: JOURNAL OF NEUROCHEMISTRY, (2000 Feb) 74 (2) 527-39.  
Journal code: 2985190R. ISSN: 0022-3042.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200002  
ENTRY DATE: Entered STN: 20000218  
Last Updated on STN: 20000218  
Entered Medline: 20000210

L3 ANSWER 5 OF 21 MEDLINE

TI Essential roles of c-JUN and c-JUN N-terminal kinase (JNK) in  
neuregulin-increased expression of the acetylcholine receptor  
epsilon-subunit.

AB Neuregulin is a neural factor implicated in upregulation of acetylcholine  
receptor (AChR) synthesis at the neuromuscular junction. Previous studies  
have demonstrated that the extracellular signal-regulated kinase (ERK)  
subgroup of MAP kinases is required for neuregulin-induced AChR gene  
expression. We report here that the neuregulin-mediated increase in AChR  
epsilon-subunit mRNA was a delayed response in C2C12 muscle cells.  
Neuregulin induced expression of immediate early genes c-jun and c-fos,  
which followed and depended on the ERK activation. Treatment of muscle  
cells with cycloheximide to inhibit c-JUN  
synthesis at the protein level and suppression of c-JUN function by a  
dominant-negative mutant blocked neuregulin-induced expression of the  
epsilon-subunit gene, indicating an essential role of c-JUN in neuregulin  
signaling. Furthermore, neuregulin activated c-JUN N-terminal kinase  
(JNK) in C2C12 muscle cells. Blockade of JNK activation by overexpressing  
dominant-negative MKK4 inhibited epsilon-promoter activation. Moreover,  
overexpression of the JNK dominant-negative mutant inhibited  
neuregulin-mediated expression of the epsilon-transgene and endogenous  
epsilon-mRNA. Taken together, our results demonstrate important roles of  
c-JUN and JNK in neuregulin-mediated expression of the AChR  
epsilon-subunit gene and suggest that neuregulin activates multiple  
signaling cascades that converge to regulate AChR epsilon-subunit gene  
expression.

ACCESSION NUMBER: 1999423887 MEDLINE  
DOCUMENT NUMBER: 99423887 PubMed ID: 10493750  
TITLE: Essential roles of c-JUN and c-JUN N-terminal kinase (JNK)  
in neuregulin-increased expression of the acetylcholine  
receptor epsilon-subunit.  
AUTHOR: Si J; Wang Q; Mei L  
CORPORATE SOURCE: Department of Pharmacology, University of Virginia School  
of Medicine, Charlottesville, Virginia 22908, USA.  
CONTRACT NUMBER: NS34062 (NINDS)  
SOURCE: JOURNAL OF NEUROSCIENCE, (1999 Oct 1) 19 (19) 8498-508.  
Journal code: 8102140. ISSN: 1529-2401.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199910  
ENTRY DATE: Entered STN: 19991026  
Last Updated on STN: 20010521  
Entered Medline: 19991014

L3 ANSWER 6 OF 21 MEDLINE

TI c-jun N-terminal kinase is involved in AUUUA-mediated interleukin-3 mRNA

turnover in mast cells.

AB Whereas signalling pathways involved in transcriptional control have been studied extensively, the pathways regulating mRNA turnover remain poorly understood. We are interested in the role of mRNA stability in cell activation and oncogenesis using PB-3c mast cells as a model system. In these cells the short-lived interleukin-3 (IL-3) mRNA is stabilized by ionomycin treatment and following oncogenesis. To identify the signalling pathways involved in these mechanisms, we analysed the effect of different kinase inhibitors. SB202190 and wortmannin were shown to antagonize ionomycin-induced IL-3 mRNA stabilization in PB-3c cells in the presence of actinomycin D, and this effect coincided with their ability to inhibit c-jun N-terminal kinase (JNK) activation by ionomycin. Moreover, transfection of activated MEKK1 amplified ionomycin-induced IL-3 mRNA expression at the post-transcriptional level, and a dominant-negative mutant of JNK counteracted mRNA stabilization by ionomycin. Taken together, these data indicate that JNK is involved in the regulation of IL-3 mRNA turnover in mast cells. In addition, transfection experiments revealed that the cis-acting AU-rich element in the 3' untranslated region of IL-3 mRNA is necessary and sufficient to confer JNK-dependent mRNA stabilization in response to cell activation.

ACCESSION NUMBER: 1998447605 MEDLINE  
DOCUMENT NUMBER: 98447605 PubMed ID: 9774347  
TITLE: c-jun N-terminal kinase is involved in AUUUA-mediated interleukin-3 mRNA turnover in mast cells.  
AUTHOR: Ming X F; Kaiser M; Moroni C  
CORPORATE SOURCE: Institute for Medical Microbiology, University of Basel, Petersplatz 10, CH-4003 Basel, Switzerland.  
SOURCE: EMBO JOURNAL, (1998 Oct 15) 17 (20) 6039-48.  
Journal code: 8208664. ISSN: 0261-4189.  
PUB. COUNTRY: ENGLAND: United Kingdom  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199812  
ENTRY DATE: Entered STN: 19990115  
Last Updated on STN: 20020420  
Entered Medline: 19981210

L3 ANSWER 7 OF 21 MEDLINE

TI Ro 09-2210 exhibits potent anti-proliferative effects on activated T cells by selectively blocking MKK activity.

AB By using high throughput screening of microbial broths, we have identified a compound, designated Ro 09-2210, which is able to block anti-CD3 induced peripheral blood T cell activation with an IC50 = 40 nM. Ro 09-2210 was also able to block antigen-induced IL-2 secretion with an IC50 = 30 nM, but was considerably less potent at blocking Ca2+ flux stimulated by anti-CD3 treatment. To determine the mechanism of action of Ro 09-2210, we set up a transient expression system in Jurkat T cells using a variety of reporter gene constructs and showed effective inhibition of phorbol ester/ionomycin-induced NF-AT activation and anti-CD3 induced NF-AT with IC50 = 7.7 and 10 nM, respectively. Ro 09-2210 was also able to inhibit phorbol ester/ionomycin-induced activation of AP1 with IC50 = <10 nM. We further showed that Ro 09-2210 was unable to inhibit c-jun induced expression of AP1-dependent reporter constructs (IC50 > 500 nM), but was able to potently inhibit ras-induced AP1 activation (IC50 = 20 nM). This suggested that Ro 09-2210 was inhibiting an activator of AP-1 which was upstream of c-jun and downstream of ras signaling. To investigate further, we then purified a number of different kinases, including PKC, PhK, ZAP-70, ERK, and MEK 1 (a MKK), and showed that Ro 09-2210 was a selective inhibitor of MEK1 in vitro (IC50 = 59 nM).

ACCESSION NUMBER: 1998313295 MEDLINE  
DOCUMENT NUMBER: 98313295 PubMed ID: 9649341  
TITLE: Ro 09-2210 exhibits potent anti-proliferative effects on

activated T cells by selectively blocking MKK activity.  
 AUTHOR: Williams D H; Wilkinson S E; Purton T; Lamont A; Flotow H; Murray E J  
 CORPORATE SOURCE: Roche Research Centre, Herts, United Kingdom.  
 SOURCE: BIOCHEMISTRY, (1998 Jun 30) 37 (26) 9579-85.  
 Journal code: 0370623. ISSN: 0006-2960.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199807  
 ENTRY DATE: Entered STN: 19980731  
 Last Updated on STN: 20020420  
 Entered Medline: 19980723

L3 ANSWER 8 OF 21 MEDLINE

TI The inhibitory activity of a transdominant c-jun mutant fused to the ligand binding domain of the estrogen receptor.  
 AB Tam-67 is an amino-terminal deletion mutant of c-Jun (delta3-122) lacking most of the c-Jun transactivation domain, which has been shown previously to function in a transdominant fashion to inhibit c-Jun-induced transactivation and cellular transformation. In order to create a ligand-dependent dominant negative repressor of AP-1, we have constructed a fusion of the TAM-67 gene with the ligand binding domain of the estrogen receptor. Fusion of TAM-67 with the ligand binding domain of the estrogen receptor produced a 68 kD protein (TAM-67ER) which was immunoprecipitated by c-Jun-specific and estrogen receptor-specific antisera and shown by gel retardation assay to bind oligonucleotides containing an AP-1 sequence. Cotransfection of TAM-67ER and an AP-1-dependent reporter construct into rat embryo cells demonstrated ligand specific inhibition of AP-1 transactivation. In the absence of hormone, TAM-67ER produced complete inhibition of c-Jun-induced AP-1 transactivation. This inhibition was relieved by treatment with estradiol but not by treatment with tamoxifen. In addition, TAM-67ER inhibited activated c-Ha-ras- or c-raf-induced transformation of NIH3T3 cells. However, this inhibition of transformation was not relieved by the addition of estrogen. Thus, TAM-67ER inhibits transactivation in a ligand-dependent manner, but inhibits transformation in a ligand-independent manner. The results suggest that the ligand-dependent transactivation domain of the estrogen receptor (TAF-2) can substitute for the c-Jun transactivation domain absent in TAM-67 to stimulate transactivation. However, TAF-2 cannot substitute for the missing c-Jun transactivation domain to induce cellular transformation.

ACCESSION NUMBER: 96243048 MEDLINE  
 DOCUMENT NUMBER: 96243048 PubMed ID: 8649795  
 TITLE: The inhibitory activity of a transdominant c-jun mutant fused to the ligand binding domain of the estrogen receptor.  
 AUTHOR: Kim S; Brown P H; Birrer M J  
 CORPORATE SOURCE: Biomarkers and Prevention Research Branch, Division of Clinical Sciences, National Cancer Institute, Rockville, Maryland 20850, USA.  
 SOURCE: ONCOGENE, (1996 Mar 7) 12 (5) 1043-53.  
 Journal code: 8711562. ISSN: 0950-9232.  
 PUB. COUNTRY: ENGLAND: United Kingdom  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199607  
 ENTRY DATE: Entered STN: 19960805  
 Last Updated on STN: 19960805  
 Entered Medline: 19960722

L3 ANSWER 9 OF 21 MEDLINE



TI Androgen receptor-mediated transcriptional regulation in the absence of direct interaction with a specific DNA element.

AB Androgen receptor (AR) brings about a ligand-dependent inhibition of low-affinity neurotrophin receptor (p75) promoter constructs in cultured cells, with the greatest inhibition being achieved with a reporter gene containing 1050 nucleotides (nt) of the promoter. The receptor domain critical for trans-repression localizes to the same region (amino acids 147-296) as that mandatory for transactivation. In contrast to trans-activation, AR does not interact directly with specific DNA elements to elicit trans-repression of p75 promoter constructs, although an intact DNA-binding domain of the receptor is required for both actions. In a search for interacting partners, both extensively purified full-length AR and AR-DNA binding domain were found to inhibit c-Jun/AP-1 site interaction without themselves binding to the AP-1 element. Prior binding of c-Jun to the AP-1 element protected the complex from the receptor's interference. Repression was not mutual, as c-Jun did not inhibit AR-androgen response element interaction or trans-activation through an androgen response element-containing promoter. The 1050-nt-long p75 promoter sequence does not contain an AP-1 element; an AP-1-like site in the vector backbone mediates the trans-repression by the AR in recipient cells. Intriguingly, an AR form with a large N-terminal deletion (the delta 46-408 mutant) behaved as a transcriptional activator of the p75 promoter through a mechanism that was also independent of specific DNA binding. Collectively, these data indicate that, in a proper context, AR is able to elicit both transrepression and trans-activation without interacting directly with specific DNA elements. Sequences responsible for the down-regulation of p75 mRNA by androgens in vivo are, however, not located in the proximal 1050 nt of the p75 promoter.

ACCESSION NUMBER: 96026867 MEDLINE  
DOCUMENT NUMBER: 96026867 PubMed ID: 7476976  
TITLE: Androgen receptor-mediated transcriptional regulation in the absence of direct interaction with a specific DNA element.  
AUTHOR: Kallio P J; Poukka H; Moilanen A; Janne O A; Palvimo J J  
CORPORATE SOURCE: Department of Physiology, University of Helsinki, Finland.  
SOURCE: MOLECULAR ENDOCRINOLOGY, (1995 Aug) 9 (8) 1017-28.  
Journal code: 8801431. ISSN: 0888-8809.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199512  
ENTRY DATE: Entered STN: 19960124  
Last Updated on STN: 20000303  
Entered Medline: 19951206

L3 ANSWER 10 OF 21 MEDLINE  
TI Mechanism of action of a dominant-negative mutant of c-Jun.  
AB The AP-1 transcriptional activating complex, made up of Jun and Fos protein, is involved in controlling many cellular processes such as cell proliferation, differentiation and transformation. We have previously characterized a dominant-negative mutant of c-Jun called TAM-67 which forms dimers with c-Jun and c-Fos, and binds DNA as a homodimer or heterodimer with c-Jun or c-Fos. This dominant-negative mutant is a potent inhibitor of AP-1 mediated transactivation, as well as c-jun/ras and TPA/ras-induced transformation. The present report describes experiments designed to elucidate the exact molecular mechanism of this dominant-negative inhibitor. The DNA binding kinetics of both TAM-67:TAM-67 homodimers as well as TAM-67:Fos heterodimers were studied and compared to those of c-Jun and other transactivation-deficient mutants of c-Jun. These studies demonstrated that the TAM-67 proteins have similar DNA binding kinetics to c-Jun and other Jun mutant proteins. Thus, the deletion of the amino-terminal end of the Jun protein does not significantly alter the protein's affinity for DNA. In addition, to

determine whether TAM-67 functions through the formation of homodimers, or through interactions with endogenous c-Jun or c-Fos, we constructed a pair of chimeric proteins made by replacing the leucine zipper of TAM-67 with the leucine zippers of GCN4 and c-Fos. These chimeric proteins, termed TAM/GCN4 and TAM/Fos, were then tested for their ability to bind DNA, **inhibit c-Jun-induced transactivation**, and inhibit TPA/ras-mediated transformation. The results of these studies show that while both chimeric proteins bind equally well to DNA, only the TAM/Fos protein, and not the TAM/GCN4 protein, inhibits AP-1-induced transactivation and TPA/ras-induced transformation. When compared to the TAM-67 protein, the TAM/Fos protein is an equally potent inhibitor of transactivation and transformation. These results suggest that TAM-67 inhibits AP-1-mediated processes through a 'quenching' mechanism by inhibiting the function of endogenous Jun and/or Fos proteins. The implications of these mechanistic findings on the development of potent inhibitors of signal transduction pathways are discussed.

ACCESSION NUMBER: 94151001 MEDLINE  
DOCUMENT NUMBER: 94151001 PubMed ID: 8108121  
TITLE: Mechanism of action of a dominant-negative mutant of c-Jun.  
AUTHOR: Brown P H; Chen T K; Birrer M J  
CORPORATE SOURCE: Biomarkers and Prevention Research Branch, National Cancer Institute, Rockville, Maryland 20850.  
SOURCE: ONCOGENE, (1994 Mar) 9 (3) 791-9.  
Journal code: 8711562. ISSN: 0950-9232.  
PUB. COUNTRY: ENGLAND: United Kingdom  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199403  
ENTRY DATE: Entered STN: 19940330  
Last Updated on STN: 20030204  
Entered Medline: 19940323

L3 ANSWER 11 OF 21 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.  
TI Functional analysis of the Rel/NF-KB and phosphatidylinositol 3-kinase/Akt survival pathways in nerve growth factor-dependent neurons.  
AB Withdrawal of nerve growth factor (NGF) from sympathetic neurons results in cell death characterized by c-Jun-N-terminal kinase (JNK) activation, translocation of Bax to mitochondria, release of cytochrome c from mitochondria, and caspase activation. Re-addition of NGF can halt JNK activation, cytochrome c release and downstream events by a mechanism that probably involves the phosphatidylinositol (PI) 3-kinase/Akt pathway and other factors. We previously showed that NF-KB activity increases in response to NGF treatment in sympathetic neurons and that a peptide inhibitor of NF-KB blocks NGF-promoted survival. In addition, expression of the c-Rel subunit of NF-KB can promote survival of neurons in the absence of NGF. Expression of c-Rel blocks cytochrome c release caused by NGF withdrawal but does not **inhibit c-Jun** phosphorylation. Conversely, inhibition of NF-KB via expression of a stabilized form of IKB promotes cytochrome c release and cell death in NGF-maintained neurons. In contrast to the effects of c-Rel, expression of activated PI 3-kinase or Akt blocks c-Jun phosphorylation with only a small effect on cytochrome c release. While expression of c-Rel protects neurons from death caused by inhibitors of PI 3-kinase or Akt, NF-KB function is not critical for Akt-promoted survival. These results suggest that the PI 3-kinase/Akt and NF-KB survival pathways target distinct cell death events in neurons. Studies underway using c-Rel knockout mice may help determine the importance of NF-KB for NGF-promoted survival.

ACCESSION NUMBER: 2001:562580 BIOSIS  
DOCUMENT NUMBER: PREV200100562580  
TITLE: Functional analysis of the Rel/NF-KB and phosphatidylinositol 3-kinase/Akt survival pathways in nerve growth factor-dependent neurons.  
AUTHOR(S): Freeman, R. S. (1); Sarmiere, P. D. (1)

CORPORATE SOURCE: (1) Department of Pharmacology and Physiology, University of Rochester, Rochester, NY USA  
SOURCE: Society for Neuroscience Abstracts, (2001) Vol. 27, No. 2, pp. 1824. print.  
Meeting Info.: 31st Annual Meeting of the Society for Neuroscience San Diego, California, USA November 10-15, 2001  
ISSN: 0190-5295.  
DOCUMENT TYPE: Conference  
LANGUAGE: English  
SUMMARY LANGUAGE: English

L3 ANSWER 12 OF 21 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.  
TI Analysis of the NF-kappaB and PI 3-kinase/Akt survival pathways in nerve growth factor-dependent neurons.  
AB Nerve growth factor (NGF) readdition to NGF-deprived neurons can halt Jun N-terminal kinase (JNK) activation, cytochrome c release, and cell death through mechanisms that may involve phosphatidylinositol (PI) 3-kinase, Akt, and nuclear factor kappa B (NF-kappaB). We found that expression of the NF-kappaB protein c-Rel in NGF-deprived neurons blocks cytochrome c release but does not inhibit c-Jun phosphorylation. Conversely, inhibition of NF-kappaB in NGF-maintained neurons promotes cytochrome c release and cell death. In contrast to c-Rel, activated PI 3-kinase and Akt inhibit c-Jun phosphorylation but have only a small effect on cytochrome c release. Finally, although c-Rel can protect neurons from death caused by inhibitors of PI 3-kinase or Akt, NF-kappaB function is not critical for Akt-promoted survival. These results suggest that the PI 3-kinase/Akt and NF-kappaB survival pathways target distinct cell death events in neurons.

ACCESSION NUMBER: 2001:548709 BIOSIS  
DOCUMENT NUMBER: PREV200100548709  
TITLE: Analysis of the NF-kappaB and PI 3-kinase/Akt survival pathways in nerve growth factor-dependent neurons.  
AUTHOR(S): Sarmiere, Patrick D.; Freeman, Robert S. (1)  
CORPORATE SOURCE: (1) Department of Pharmacology and Physiology, University of Rochester School of Medicine, 601 Elmwood Avenue, Rochester, NY, 14642: Robert\_Freeman@URMC.Rochester.edu USA  
SOURCE: Molecular and Cellular Neuroscience, (September, 2001) Vol. 18, No. 3, pp. 320-331. print.  
ISSN: 1044-7431.  
DOCUMENT TYPE: Article  
LANGUAGE: English  
SUMMARY LANGUAGE: English

L3 ANSWER 13 OF 21 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.  
TI Inhibition of JNK by overexpression of the JNK binding domain of JIP-1 prevents apoptosis in sympathetic neurons.  
AB Studies in non-neuronal cells show that c-Jun N-terminal kinases (JNK) play a key role in apoptotic cell death. In some neurons JNK is also thought to initiate cell death by the activation of c-Jun. JNK inhibition has been achieved pharmacologically by inhibiting upstream kinases, but there has been no direct demonstration that inhibition of JNK can prevent neuronal death. We have therefore examined whether the JNK binding domain (JBD) of JNK-interacting protein-1 (JIP-1, a scaffold protein and specific inhibitor of JNK) can inhibit c-Jun phosphorylation and support the survival of sympathetic neurons deprived of NGF. We show that expression of the JBD in >80% of neurons was sufficient to prevent the phosphorylation of c-Jun and its nuclear accumulation as well as abrogate neuronal cell death induced by NGF deprivation. JBD expression also preserved the capacity of mitochondria to reduce MTT. Interestingly, although the PTB domain of JIP was reported to interact with rhoGEF, expression of the JBD domain was sufficient to localize the protein to the membrane cortex and growth cones. Hence, JNK activation is a key event in apoptotic death induced by NGF withdrawal,

where its point of action lies upstream of mitochondrial dysfunction.

ACCESSION NUMBER: 2001:215147 BIOSIS  
DOCUMENT NUMBER: PREV200100215147  
TITLE: Inhibition of JNK by overexpression of the JNK binding domain of JIP-1 prevents apoptosis in sympathetic neurons.  
AUTHOR(S): Harding, Thomas C.; Xue, Luzheng; Bienemann, Ali; Haywood, Darren; Dickens, Martin; Tolkovsky, Aviva M.; Uney, James B. (1)  
CORPORATE SOURCE: (1) University Research Centre for Neuroendocrinology and MRC Centre for Synaptic Plasticity, University of Bristol, Marlborough Street, Bristol, BS2 8HW:  
amt@mole.bio.cam.ac.uk, james.uney@bristol.ac.uk UK  
SOURCE: Journal of Biological Chemistry, (February 16, 2001) Vol. 276, No. 7, pp. 4531-4534. print.  
ISSN: 0021-9258. *Isabel date*  
DOCUMENT TYPE: Article  
LANGUAGE: English  
SUMMARY LANGUAGE: English

L3 ANSWER 14 OF 21 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

TI Insulin-like growth factor-I and Bcl-XL inhibit c-jun N-terminal kinase activation and rescue Schwann cells from apoptosis.

AB We previously reported that Schwann cells undergo apoptosis after serum withdrawal. Insulin-like growth factor-I, via phosphatidylinositol-3 kinase, inhibits caspase activation and rescues Schwann cells from serum withdrawal-induced apoptosis. In this study, we examined the role of c-jun N-terminal protein kinase (JNK) in Schwann cell apoptosis induced by serum withdrawal. Activation of both JNK1 and JNK2 was detected 1 h after serum withdrawal with the maximal level detected at 2 h. A dominant negative JNK mutant, JNK (APF), blocked JNK activation induced by serum withdrawal and Schwann cell apoptosis, suggesting JNK activation participates in Schwann cell apoptosis. Serum withdrawal-induced JNK activity was caspase dependent and inhibited by a caspase 3 inhibitor, Ac-DEVD-CHO. Because insulin-like growth factor-I and Bcl-XL are both Schwann cell survival factors, we tested their effects on JNK activation during apoptosis. Insulin-like growth factor-I treatment decreased both JNK1 and JNK2 activity induced by serum withdrawal. LY294002, a phosphatidylinositol-3 kinase inhibitor, blocked insulin-like growth factor-I inhibition on JNK activation, suggesting that phosphatidylinositol-3 kinase mediates the effects of insulin-like growth factor-I. Overexpression of Bcl-XL also resulted in less Schwann cell death and inhibition of JNK activation after serum withdrawal. Collectively, these results suggest JNK activation is involved in Schwann cell apoptosis induced by serum withdrawal. Insulin-like growth factor-I and Bcl family proteins rescue Schwann cells, at least in part, by inhibition of JNK activity.

ACCESSION NUMBER: 2001:141072 BIOSIS  
DOCUMENT NUMBER: PREV200100141072  
TITLE: Insulin-like growth factor-I and Bcl-XL inhibit c-jun N-terminal kinase activation and rescue Schwann cells from apoptosis.  
AUTHOR(S): Cheng, Hsin-Lin; Steinway, Matthew L.; Xin, Xiping; Feldman, Eva L. (1)  
CORPORATE SOURCE: (1) Department of Neurology, University of Michigan, 200 Zina Pitcher Place, 4414 Kresge III, Ann Arbor, MI, 48109-0588: efeldman@umich.edu USA  
SOURCE: Journal of Neurochemistry, (February, 2001) Vol. 76, No. 3, pp. 935-943. print.  
ISSN: 0022-3042.  
DOCUMENT TYPE: Article  
LANGUAGE: English  
SUMMARY LANGUAGE: English

L3 ANSWER 15 OF 21 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

TI Functional interplay between nuclear factor-kappaB and c-Jun integrated by coactivator p300 determines the survival of nerve growth factor-dependent PC12 cells.

AB Nerve growth factor (NGF) activates the transcription factors nuclear factor kappaB (NF-kappaB) and activator protein-1 (AP-1) in sympathetic neurons. Whereas NGF-inducible NF-kappaB is required for the survival of neurons, c-Jun has the ability to promote neuronal death. In this report, we have examined the effect of NGF withdrawal on c-Jun and NF-kappaB transcription factors in PC12 cells differentiated to a neuronal phenotype. We show that the withdrawal of NGF from these cultures results in de novo synthesis of c-Jun, increase in AP-1 activity, and down-regulation of NF-kappaB activity. To investigate how the signal transduction pathways activating c-Jun and NF-kappaB are differentially regulated by NGF, we performed transcriptional analyses. Expression of ReIA (NF-kappaB) suppressed the c-Jun-dependent transcription of c-jun, and this effect was reversed by overexpression of the coactivator p300. ReIA's effects on c-Jun transcription were mediated by competitive binding of the carboxy-terminal region of ReIA to the CH1 domain of p300, which also binds to c-Jun; deletion of this region abrogated the ability of ReIA to inhibit c-Jun activity. Furthermore, the inhibition of endogenous NF-kappaB in NGF-maintained neuronal PC12 cells led to the induction of c-Jun synthesis and a marked increase in cell death. Together, these studies demonstrate a functional interaction between NF-kappaB and c-Jun and suggest a novel mechanism of NF-kappaB-mediated neuroprotection.

ACCESSION NUMBER: 2000:99787 BIOSIS

DOCUMENT NUMBER: PREV200000099787

TITLE: Functional interplay between nuclear factor-kappaB and c-Jun integrated by coactivator p300 determines the survival of nerve growth factor-dependent PC12 cells.

AUTHOR(S): Maggirwar, Sanjay B. (1); Ramirez, Servio; Tong, Ning; Gelbard, Harris A.; Dewhurst, Stephen

CORPORATE SOURCE: (1) Department of Microbiology and Immunology, University of Rochester Medical Center, 575 Elmwood Avenue, Rochester, NY, 14642 USA

SOURCE: Journal of Neurochemistry, (Feb., 2000) Vol. 74, No. 2, pp. 527-539.

ISSN: 0022-3042.

DOCUMENT TYPE: Article

LANGUAGE: English

SUMMARY LANGUAGE: English

L3 ANSWER 16 OF 21 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

TI Essential roles of c-JUN and c-JUN N-terminal kinase (JNK) in neuregulin-increased expression of the acetylcholine receptor epsilon-subunit.

AB Neuregulin is a neural factor implicated in upregulation of acetylcholine receptor (AChR) synthesis at the neuromuscular junction. Previous studies have demonstrated that the extracellular signal-regulated kinase (ERK) subgroup of MAP kinases is required for neuregulin-induced AChR gene expression. We report here that the neuregulin-mediated increase in AChR epsilon-subunit mRNA was a delayed response in C2C12 muscle cells. Neuregulin induced expression of immediate early genes c-jun and c-fos, which followed and depended on the ERK activation. Treatment of muscle cells with cycloheximide to inhibit c-JUN synthesis at the protein level and suppression of c-JUN function by a dominant-negative mutant blocked neuregulin-induced expression of the epsilon-subunit gene, indicating an essential role of c-JUN in neuregulin signaling. Furthermore, neuregulin activated c-JUN N-terminal kinase (JNK) in C2C12 muscle cells. Blockade of JNK activation by overexpressing dominant-negative MKK4 inhibited epsilon-promoter activation. Moreover, overexpression of the JNK dominant-negative mutant inhibited neuregulin-mediated expression of the epsilon-transgene and endogenous epsilon-mRNA. Taken together, our results demonstrate important roles of

c-JUN and JNK in neuregulin-mediated expression of the AChR epsilon-subunit gene and suggest that neuregulin activates multiple signaling cascades that converge to regulate AChR epsilon-subunit gene expression.

ACCESSION NUMBER: 2000:79801 BIOSIS  
DOCUMENT NUMBER: PREV200000079801  
TITLE: Essential roles of c-JUN and c-JUN N-terminal kinase (JNK) in neuregulin-increased expression of the acetylcholine receptor epsilon-subunit.  
AUTHOR(S): Si, Jutong; Wang, Qi; Mei, Lin (1)  
CORPORATE SOURCE: (1) Department of Neurobiology, University of Alabama at Birmingham, 1530 3rd Avenue South, CIRC 5th Floor, Birmingham, AL USA  
SOURCE: Journal of Neuroscience, (Oct. 1 ) Vol. 19, No. 19, pp. 8498-8508.  
ISSN: 0270-6474.  
DOCUMENT TYPE: Article  
LANGUAGE: English  
SUMMARY LANGUAGE: English

L3 ANSWER 17 OF 21 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. '  
TI c-jun N-terminal kinase is involved in AUUUA-mediated interleukin-3 mRNA turnover in mast cells.  
AB Whereas signalling pathways involved in transcriptional control have been studied extensively, the pathways regulating mRNA turnover remain poorly understood. We are interested in the role of mRNA stability in cell activation and oncogenesis using PB-3c mast cells as a model system. In these cells the short-lived interleukin-3 (IL-3) mRNA is stabilized by ionomycin treatment and following oncogenesis. To identify the signalling pathways involved in these mechanisms, we analysed the effect of different kinase inhibitors. SB202190 and wortmannin were shown to antagonize ionomycin-induced IL-3 mRNA stabilization in PB-3c cells in the presence of actinomycin D, and this effect coincided with their ability to inhibit c-jun N-terminal kinase (JNK) activation by ionomycin. Moreover, transfection of activated MEKK1 amplified ionomycin-induced IL-3 mRNA expression at the post-transcriptional level, and a dominant-negative mutant of JNK counteracted mRNA stabilization by ionomycin. Taken together, these data indicate that JNK is involved in the regulation of IL-3 mRNA turnover in mast cells. In addition, transfection experiments revealed that the cis-acting AU-rich element in the 3' untranslated region of IL-3 mRNA is necessary and sufficient to confer JNK-dependent mRNA stabilization in response to cell activation.

ACCESSION NUMBER: 1998:511388 BIOSIS  
DOCUMENT NUMBER: PREV199800511388  
TITLE: c-jun N-terminal kinase is involved in AUUUA-mediated interleukin-3 mRNA turnover in mast cells.  
AUTHOR(S): Ming, Xiu-Fen; Kaiser, Mirjam; Moroni, Christoph (1)  
CORPORATE SOURCE: (1) Inst. Med. Microbiol., Univ. Basel, Petersplatz 10, CH-4003 Basel Switzerland  
SOURCE: EMBO (European Molecular Biology Organization) Journal, (Oct. 15, 1998) Vol. 17, No. 20, pp. 6039-6048.  
ISSN: 0261-4189.  
DOCUMENT TYPE: Article  
LANGUAGE: English

L3 ANSWER 18 OF 21 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.  
TI Ro 09-2210 exhibits potent anti-proliferative effects on activated T cells by selectively blocking MKK activity.  
AB By using high throughput screening of microbial broths, we have identified a compound, designated Ro 09-2210, which is able to block anti-CD3 induced peripheral blood T cell activation with an IC50 = 40 nM. Ro 09-2210 was also able to block antigen-induced IL-2 secretion with an IC50 = 30 nM, but was considerably less potent at blocking Ca2+ flux stimulated by

anti-CD3 treatment. To determine the mechanism of action of Ro 09-2210, we set up a transient expression system in Jurkat T cells using a variety of reporter gene constructs and showed effective inhibition of phorbol ester/ionomycin-induced NF-AT activation and anti-CD3-induced NF-AT with IC50 = 7.7 and 10 nM, respectively. Ro 09-2210 was also able to inhibit phorbol ester/ionomycin-induced activation of AP1 with IC50 = < 10 nM. We further showed that Ro 09-2210 was unable to **inhibit c-jun** induced expression of AP1-dependent reporter constructs (IC50 > 500 nM), but was able to potently inhibit ras-induced AP1 activation (IC50 = 20 nM). This suggested that Ro 09-2210 was inhibiting an activator of AP-1 which was upstream of c-jun and downstream of ras signaling. To investigate further, we then purified a number of different kinases, including PKC, PhK, ZAP-70, ERK, and MEK 1 (a MKK), and showed that Ro 09-2210 was a selective inhibitor of MEK1 in vitro (IC50 = 59 nM).

ACCESSION NUMBER: 1998:349893 BIOSIS  
DOCUMENT NUMBER: PREV199800349893  
TITLE: Ro 09-2210 exhibits potent anti-proliferative effects on activated T cells by selectively blocking MKK activity.  
AUTHOR(S): Williams, D. H.; Wilkinson, S. E.; Purton, T.; Lamont, A.; Flotow, H.; Murray, E. J. (1)  
CORPORATE SOURCE: (1) Roche Res. Centre, P.O. Box 8, Welwyn Garden City, Herts AL7 3AU UK  
SOURCE: Biochemistry, (June 30, 1998) Vol. 37, No. 26, pp. 9579-9585.  
ISSN: 0006-2960.  
DOCUMENT TYPE: Article  
LANGUAGE: English

L3 ANSWER 19 OF 21 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.  
TI The inhibitory activity of a transdominant c-jun mutant fused to the ligand binding domain of the estrogen receptor.  
AB Tam-67 is an amino-terminal deletion mutant of c-Jun (DELTA-3-122) lacking most of the c-Jun transactivation domain, which has been shown previously to function in a transdominant fashion to **inhibit c-Jun**-induced transactivation and cellular transformation. In order to create a ligand-dependent dominant negative repressor of AP-1, we have constructed a fusion of the TAM-67 gene with the ligand binding domain of the estrogen receptor. Fusion of TAM-67 with the ligand binding domain of the estrogen receptor produced a 68 kD protein (TAM67ER) which was immunoprecipitated by c-Jun-specific and estrogen receptor-specific antisera and shown by gel retardation assay to bind oligonucleotides containing an AP-1 sequence. Cotransfection of TAM-67ER and an AP-1-dependent reporter construct into rat embryo cells demonstrated ligand specific inhibition of AP-1 transactivation. In the absence of hormone, TAM-67ER produced complete inhibition of c-Jun-induced AP-1 transactivation. This inhibition was relieved by treatment with estradiol but not by treatment with tamoxifen. In addition, TAM-67ER inhibited activated c-Ha-ras- or c-raf-induced transformation of NIH3T3 cells. However, this inhibition of transformation was not relieved by the addition of estrogen. Thus, TAM-67ER inhibits transactivation in a ligand-dependent manner, but inhibits transformation in a ligand-independent manner. The results suggest that the ligand-dependent transactivation domain of the estrogen receptor (TAF-2) can substitute for the c-Jun transactivation domain absent in TAM-67 to stimulate transactivation. However, TAF-2 cannot substitute for the missing c-Jun transactivation domain to induce cellular transformation.

ACCESSION NUMBER: 1996:189958 BIOSIS  
DOCUMENT NUMBER: PREV199698746087  
TITLE: The inhibitory activity of a transdominant c-jun mutant fused to the ligand binding domain of the estrogen receptor.  
AUTHOR(S): Kim, Sung; Brown, Powel H.; Birrer, Michael J. (1)  
CORPORATE SOURCE: (1) Biomarkers Prevention Res. Branch, Div. Clin. Sci., Natl. Cancer Inst., 9610 Medical Center Dr., Room 300,

Rockville, MD 20850 USA  
SOURCE: Oncogene, (1996) Vol. 12, No. 5, pp. 1043-1053.  
ISSN: 0950-9232.  
DOCUMENT TYPE: Article  
LANGUAGE: English

L3 ANSWER 20 OF 21 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.  
TI Androgen receptor-mediated transcriptional regulation in the absence of direct interaction with a specific DNA element.  
AB Androgen receptor (AR) brings about a ligand-dependent inhibition of low-affinity neurotrophin receptor (p75) promoter constructs in cultured cells, with the greatest inhibition being achieved with a reporter gene containing 1050 nucleotides (nt) of the promoter. The receptor domain critical for trans-repression localizes to the same region (amino acids 147-296) as that mandatory for transactivation. In contrast to trans-activation, AR does not interact directly with specific DNA elements to elicit trans-repression of p75 promoter constructs, although an intact DNA-binding domain of the receptor is required for both actions. In a search for interacting partners, both extensively purified full-length AR and AR-DNA binding domain were found to **inhibit c-Jun/AP-1** site interaction without themselves binding to the AP-1 element. Prior binding of c-Jun to the AP-1 element protected the complex from the receptor's interference. Repression was not mutual, as c-Jun did not inhibit AR-androgen response element interaction or trans-activation through an androgen response element-containing promoter. The 1050-nt-long p75 promoter sequence does not contain an AP-1 element; an AP-1-like site in the vector backbone mediates the trans-repression by the AR in recipient cells. Intriguingly, an AR form with a large N-terminal deletion (the DELTA-46-408 mutant) behaved as a transcriptional activator of the p75 promoter through a mechanism that was also independent of specific DNA binding. Collectively, these data indicate that, in a proper context, AR is able to elicit both transrepression and trans-activation without interacting directly with specific DNA elements. Sequences responsible for the down-regulation of p75 mRNA by androgens in vivo are, however, not located in the proximal 1050 nt of the p75 promoter.

ACCESSION NUMBER: 1995:437182 BIOSIS  
DOCUMENT NUMBER: PREV199598451482  
TITLE: Androgen receptor-mediated transcriptional regulation in the absence of direct interaction with a specific DNA element.  
AUTHOR(S): Kallio, Pekka J.; Poukka, Hetti; Moilanen, Anu; Janne, Olli A.; Palvimo, Jorma J. (1)  
CORPORATE SOURCE: (1) Inst. Biomed., Dep. Physiol., P.O. Box 9, Univ. Helsinki, FIN-00014 Helsinki Finland  
SOURCE: Molecular Endocrinology, (1995) Vol. 9, No. 8, pp. 1017-1028.  
ISSN: 0888-8809.  
DOCUMENT TYPE: Article  
LANGUAGE: English

L3 ANSWER 21 OF 21 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.  
TI Mechanism of action of a dominant-negative mutant of c-Jun.  
AB The AP-1 transcriptional activating complex, made up of Jun and Fos proteins, is involved in controlling many cellular processes such as cell proliferation, differentiation and transformation. We have previously characterized a dominant-negative mutant of c-Jun called TAM-67 which forms dimers with c-Jun and c-Fos, and binds DNA as a homodimer or heterodimer with c-Jun or c-Fos. This dominant-negative mutant is a potent inhibitor of AP-1 mediated transactivation, as well as c-jun/ras and TPA/ras-induced transformation. The present report describes experiments designed to elucidate the exact molecular mechanism of this dominant-negative inhibitor. The DNA binding kinetics of both TAM-67:TAM-67 homodimers as well as TAM-67:Fos heterodimers were studied and compared to those of c-Jun and other transactivation-deficient mutants



of c-Jun. These studies demonstrated that the TAM-67 proteins have similar DNA binding kinetics to c-Jun and other Jun mutant proteins. Thus, the deletion of the amino-terminal end of the Jun protein does not significantly alter the protein's affinity for DNA. In addition, to determine whether TAM-67 functions through the formation of homodimers, or through interactions with endogenous c-Jun or c-Fos, we constructed a pair of chimeric proteins made by replacing the leucine zipper of TAM-67 with the leucine zippers of GCN4 and c-Fos. These chimeric proteins, termed TAM/GCN4 and TAM/Fos, were then tested for their ability to bind DNA, inhibit c-Jun-induced transactivation, and inhibit TPA/ras-mediated transformation. The results of these studies show that while both chimeric proteins bind equally well to DNA, only the TAM/Fos protein, and not the TAM/GCN4 protein, inhibits AP-1-induced transactivation and TPA/ras-induced transformation. When compared to the TAM-67 protein, the TAM/Fos protein is an equally potent inhibitor of transactivation and transformation. These results suggest that TAM-67 inhibits AP-1-mediated processes through a 'quenching' mechanism by inhibiting the function of endogenous Jun and/or Fos proteins. The implications of these mechanistic findings on the development of potent inhibitors of signal transduction pathways are discussed.

ACCESSION NUMBER: 1994:162506 BIOSIS  
DOCUMENT NUMBER: PREV199497175506  
TITLE: Mechanism of action of a dominant-negative mutant of c-Jun.  
AUTHOR(S): Brown, P. H.; Chen, T. K.; Birrer, M. J. (1)  
CORPORATE SOURCE: (1) Biomarkers and Prevention Research Branch, Division  
Cancer Prevention and Control, National Cancer Institute,  
9610 Medical Center Drive, Suite 300, Rockville, MD 20850  
USA  
SOURCE: Oncogene, (1994) Vol. 9, No. 3, pp. 791-799.  
ISSN: 0950-9232.  
DOCUMENT TYPE: Article  
LANGUAGE: English

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structures available in REGISTRY  
NEWS 31 Apr 11 Display formats in DGENE enhanced  
NEWS 32 Apr 14 MEDLINE Reload  
NEWS 33 Apr 17 Polymer searching in REGISTRY enhanced  
NEWS 34 Apr 21 Indexing from 1947 to 1956 being added to records in CA/CAPLUS  
NEWS 35 Apr 21 New current-awareness alert (SDI) frequency in  
WPIDS/WPINDEX/WPIX  
NEWS 36 Apr 28 RDISCLOSURE now available on STN  
NEWS 37 May 05 Pharmacokinetic information and systematic chemical names  
added to PHAR  
  
NEWS EXPRESS April 4 CURRENT WINDOWS VERSION IS V6.01a, CURRENT  
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AND CURRENT DISCOVER FILE IS DATED 01 APRIL 2003  
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=> s whi-p131  
L1 52 WHI-P131

=> s jak-3 inhibitors  
L2 11 JAK-3 INHIBITORS

=> s graft versus host disease  
L3 73225 GRAFT VERSUS HOST DISEASE

=> d l1 ti abs ibib 1-10

L1 ANSWER 1 OF 52 WPIDS (C) 2003 THOMSON DERWENT  
TI Use of inhibitors of Janus kinase/signal transducers and activators of transcription for inhibiting onset and progression of degenerative joint diseases or disorders such as osteoarthritis, rheumatoid arthritis.  
AN 2001-465338 [50] WPIDS

AB WO 200152892 A UPAB: 20010905

NOVELTY - Use of JAK/STAT (Janus kinase/signal transducers and activators of transcription) inhibitor other than debromohymenialdisine (DBH) and hymenialdisine (H) for inhibiting progression or likelihood of developing disease involving cartilage degradation, regulating expression of cartilage degrading enzyme in cell and regulating expression of pro-inflammatory agent or cytokine in a chondrocyte, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) treating (M) a JAK/STAT-mediated disease or disorder other than osteoarthritis (OA) or protein kinase C (PKC)-mediated inflammation by administering DBH or H; and

(2) an assay for detecting compounds useful for treating a disease or disorder involving cartilage degradation, by contacting JAK3 with a candidate compound and detecting a decrease in JAK3 activity.

ACTIVITY - Antiarthritic; antirheumatic; osteopathic; cytostatic; protozoacide; antileprotic; antiallergic; virucide; antiasthmatic; immunosuppressive; antiinflammatory; vasotropic; dermatological.

MECHANISM OF ACTION - Inhibitor of JAK3.

Inhibition of various OA-associated mRNAs by JAK3-specific inhibitor, WHI-P131 was evaluated. Normal human articular chondrocytes were isolated from cartilage slices and cultured. Test cultures were rinsed in PBS, and preincubated for 2 hours with 10 ml of serum-free Dulbecco's modified Eagle medium (DMEM) containing 5 micro M WHI-P131. An additional 10 ml of serum-free DMEM containing 5 micro M WHI-P131, 4 ng/ml recombinant human interleukin-1 beta (rhIL-1 beta ) and 2% antibiotic solution was then added. Two control cultures were run in parallel, one without WHI-P131 and other without WHI-P131 or rhIL-1 beta . Human DNA probes for stromelysin-1 (matrix metalloproteinase-3, MMP3), collagenase 1 (MMP1), cyclooxygenase II (COX2), NF-kappaB (p65), tumor necrosis factor- alpha (TNF- alpha ) and IL-6 were labeled with ( alpha -32P)-dCTP and used for northern blot hybridization experiments. Two concentrations of WHI-P131, 33.6 micro M and 168 micro M solubilized in DMSO, were tested. Results of the northern blot experiment demonstrated that both the 33.6 micro M and 168 micro M treatment of WHI-P131, inhibited the IL-1 beta -induced upregulation of mRNA associated with the pathology of osteoarthritis i.e. MMP3, MMP1, COX2 and p65.

USE - JAK3/STAT inhibitor is useful for inhibiting progression or likelihood of developing osteoarthritis or rheumatoid arthritis. (M) is useful for treating JAK/STAT-mediated disease or disorder, such as T cell-, mass cell-mediated disease or disorder, a type 2 disease or disorder, lymphoma B cell and a myeloid disease or disorder (claimed). T cell-mediated disorders include human T-cell leukemia/lymphoma virus (HTLV)-1, szory's syndrome, c-abl transformation, natural killer-like T cell lymphomas (NK-like tumors) and graft-vs-host disease, type 2 (cytokine hypersensitivity) diseases or disorders include leishmanias, leprosy, allergy and viral infections, mass cell-mediated disorders include allergies, hay fever, asthma, hives and anaphylaxis, and leukemias and lymphomas including acute lymphocytic and lymphoblastic leukemias, B cell lymphomas and leukemias of myeloid origin. DBH and H are useful as therapeutic agents in cancers in which JAK3 plays a role in the initiation or progression of tumorigenesis.

Dwg.0/10

ACCESSION NUMBER: 2001-465338 [50] WPIDS

DOC. NO. CPI: C2001-140486

TITLE: Use of inhibitors of Janus kinase/signal transducers and activators of transcription for inhibiting onset and progression of degenerative joint diseases or disorders such as osteoarthritis, rheumatoid arthritis.

DERWENT CLASS: B04 D16

INVENTOR(S): VASIOS, G

PATENT ASSIGNEE(S): (GENZ) GENZYME CORP

COUNTRY COUNT: 94  
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001052892	A2	20010726	(200150)*	EN	55
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW					
AU 2001029687	A	20010731	(200171)		
EP 1250137	A2	20021023	(200277)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR					

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001052892	A2	WO 2001-US2033	20010122
AU 2001029687	A	AU 2001-29687	20010122
EP 1250137	A2	EP 2001-942563	20010122
		WO 2001-US2033	20010122

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2001029687	A Based on	WO 200152892
EP 1250137	A2 Based on	WO 200152892

PRIORITY APPLN. INFO: US 2000-723490 20001128; US 2000-177872P  
20000124

L1 ANSWER 2 OF 52 WPIDS (C) 2003 THOMSON DERWENT  
TI New quinazoline-4-substituted phenyl derivative useful for treating or preventing a disease or condition of platelet aggregation e.g. embolus formation.  
AN 2001-465078 [50] WPIDS  
CR 2002-508476 [54]  
AB WO 200145641 A UPAB: 20030204  
NOVELTY - Quinazoline-4-substituted phenyl derivative (I) or its salts are new.

DETAILED DESCRIPTION - Quinazoline-4-substituted phenyl derivative of formula (I) or its salt is new:

X = NH, R11N, S, O, CH2 or R11CH (preferably NH);  
R11 = (1-4C)alkyl or alkanoyl;  
R1 - R5 = H, OH, or halo;  
R6 - R8 = H, OH, mercapto, amino, nitro, 1-4C alkyl, 1-4C alkoxy, 1-4C alkylthio or halo; and  
R9 - R10 = H, R11, (1-4C) alkoxy, or halo.  
With the proviso that at least one of R1 - R5 is hydroxy and R9 and R10 together are methylenedioxy.

An INDEPENDENT CLAIM is also included for a therapeutic method for treating or preventing a disease or condition of platelet aggregation involves administering (I) or a composition containing to the subject.

ACTIVITY - Antianginal; Cardiant; Anticoagulant; Thrombolytic; Gynecological; Vasotropic; Cerebroprotective.

MECHANISM OF ACTION - Janus-family kinase (JAK) inhibitor; Inhibitor of signal transducers and activators of transcription (STAT-3) that associates with JAK-3 including STAT-3 alpha (p92) and STAT-3 beta (p83) isoforms; Thrombin induced platelet aggregation inhibitor.

Whole cell lysates from platelets treated with WHI-P131/DMSO stimulated with 0.1 U/ml thrombin or 10 psi g/ml collagen were collected and boiled in SDS, fractionated on an 8 % polyacrylamide gel and transferred to PVDF membranes. The membranes were subjected to Western blot analysis utilizing antibodies, which recognize all phosphorylated isoforms of STAT-3 and phosphotyrosine. WHI-P131 inhibited thrombin induced STAT-3 beta tyrosin phosphorylation and overall tyrosine phosphorylation.

USE - For treating or preventing a disease or condition of platelet aggregation including hematopoietic and cerebrovascular such as embolus formation, thrombolytic complications, disseminated intravascular comgelophthy, thrombosis, coronary heart disease, thromboembolic complications, myocardial infarction, restenosis, or atrial thrombosis formation in atrial fibrillation (claimed), chronic unstable angina, transient ischemic attacks and strokes, peripheral vascular disease, arterial thrombosis, preeclampsia, embolism, thrombosis following angioplasty, carotid endarterectomy, anastomosis of vascular grafts, or chronic exposure to cardiovascular devices.

ADVANTAGE - The compound inhibits platelet aggregation such as thrombin induced platelet aggregation. The method results in at least a 10 % reduction in thrombin-induced platelet aggregation e.g. 15, 20, 25, 30, 40, 50, 60, 70, 80, 90, 100 (preferably 90) %, or at least a 10% reduction in thrombin-induced tyrosine phosphorylation of STAT-3 beta , e.g. 15, 20, 25, 30, 40, 50, 60, 70, 80, 90, 100%.

Dwg.0/2

ACCESSION NUMBER: 2001-465078 [50] WPIDS  
 CROSS REFERENCE: 2002-508476 [54]  
 DOC. NO. CPI: C2001-140410  
 TITLE: New quinazoline-4-substituted phenyl derivative useful for treating or preventing a disease or condition of platelet aggregation e.g. embolus formation.  
 DERWENT CLASS: B02  
 INVENTOR(S): UCKUN, F M  
 PATENT ASSIGNEE(S): (PARK-N) PARKER HUGHES INST  
 COUNTRY COUNT: 94  
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001045641	A2	20010628	(200150)*	EN	24
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
AU 2001049032	A	20010703	(200164)		
US 2003013728	A1	20030116	(200308)		

#### APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001045641	A2	WO 2000-US42345	20001129
AU 2001049032	A	AU 2001-49032	20001129
US 2003013728	A1	US 1999-168179P	19991130
	Cont of	WO 2000-US42345	20001129
		US 2002-157474	20020528

#### FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2001049032	A Based on	WO 200145641

PRIORITY APPLN. INFO: US 1999-168179P 19991130; US 2002-157474  
20020528

L1 ANSWER 3 OF 52 WPIDS (C) 2003 THOMSON DERWENT  
TI Treating immediate hypersensitivity reactions or inhibiting mast-cell  
mediated allergic reactions, e.g. anaphylaxis, allergic rhinitis or  
asthma, comprises administering a Janus Kinase-3 (JAK-3) tyrosine kinase  
inhibitor .

AN 2001-201837 [20] WPIDS

CR 2000-451222 [39]; 2000-451223 [39]; 2002-065579 [09]; 2002-088962 [12];  
2002-443753 [47]; 2003-174595 [17]

AB US 6177433 B UPAB: 20030312

NOVELTY - Treating immediate hypersensitivity reaction comprises  
administering a Janus kinase 3 (JAK-3) tyrosine kinase inhibitor (I).  
comprising allergic urticaria, angioedema, allergic asthma or  
allergic reaction to insect bites, food, drugs or pollen, preferably by  
preventing the immediate hypersensitivity reaction, and inhibiting  
mast-cell mediated allergic reactions.

ACTIVITY - Antiallergic; anti-anaphylactic; immunosuppressive;  
dermatological; antiinflammatory; vasotropic.

The efficacy of P131 was tested in a model of IgE/antigen-induced  
active systemic anaphylaxis. Mice were injected with 100 mg/kg doses of  
BSA (bovine serum albumin) in 200 microliters of an aluminum hydroxide gel  
to trigger a BSA-specific IgE response. Ten days later, the BSA-sensitized  
mice were treated with two doses of P131 (45 mg/kg) or the vehicle 30  
minutes apart and then the mice were rechallenged with a 10 mg/kg  
injection of BSA to induce anaphylaxis. Eight of the fifteen (53%)  
BSA-sensitized mice that were treated with P131 prior to antigen challenge  
survived without any signs of anaphylaxis, whereas all 12 (100%) of the  
control mice developed anaphylaxis within 45 minutes after antigen  
challenge.

MECHANISM OF ACTION - JAK-3 tyrosine kinase inhibitors inhibit mast  
cell activation and degranulation and proinflammatory mediator release.

USE - The compounds are used for treatment of immediate  
hypersensitivity reaction comprising anaphylaxis, allergic rhinitis,  
allergic urticaria, angioedema, allergic asthma or allergic reaction to  
insect bites, food, drugs or pollen, preferably by preventing the  
immediate hypersensitivity reaction, and inhibiting mast-cell mediated  
allergic reactions.

DESCRIPTION OF DRAWING(S) - The figures show the effect of JAK-3  
inhibitor WHI-P131 on IgE receptor/FcERI-mediated mast  
cell responses. Figure 11A shows the effects on mast cell degeneration,  
figure 11b shows the leukotriene C4 responses.

Dwg.14E/15

ACCESSION NUMBER: 2001-201837 [20] WPIDS

CROSS REFERENCE: 2000-451222 [39]; 2000-451223 [39]; 2002-065579 [09];  
2002-088962 [12]; 2002-443753 [47]; 2003-174595 [17]

DOC. NO. CPI: C2001-059872

TITLE: Treating immediate hypersensitivity reactions or  
inhibiting mast-cell mediated allergic reactions, e.g.  
anaphylaxis, allergic rhinitis or asthma, comprises  
administering a Janus Kinase-3 (JAK-3) tyrosine kinase  
inhibitor .

DERWENT CLASS: B02

INVENTOR(S): MALAVIA, R; SUDBECK, E A; UCKUN, F M

PATENT ASSIGNEE(S): (PARK-N) PARKER HUGHES INST

COUNTRY COUNT: 1

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 6177433	B1	20010123	(200120)*		42

## APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 6177433	B1 Cont of	US 1999-263420	19990305
		US 1999-443847	19991119

PRIORITY APPLN. INFO: US 1999-263420 19990305; US 1999-443847  
19991119

L1 ANSWER 4 OF 52 MEDLINE

TI Structure-based design of novel anticancer agents.

AB Recently identified agents that interact with cytoskeletal elements such as tubulin include synthetic spiroketal pyrans (SPIKET) and monotetrahydrofuran compounds (COBRA compounds). SPIKET compounds target the spongistatin binding site of beta-tubulin and COBRA compounds target a unique binding cavity on alpha-tubulin. At nanomolar concentrations, the SPIKET compound SPIKET-P causes tubulin depolymerization and exhibits potent cytotoxic activity against cancer cells. COBRA-1 inhibits GTP-induced tubulin polymerization. Treatment of human breast cancer and brain tumor cells with COBRA-1 caused destruction of microtubule organization and apoptosis. Other studies have identified some promising protein tyrosine kinase inhibitors as anti-cancer agents. These include EGFR inhibitors such as the quinazoline derivative WHI-P97 and the leflunomide metabolite analog LFM-A12. Both LFM-A12 and WHI-P97 inhibit the in vitro invasiveness of EGFR positive human breast cancer cells at micromolar concentrations and induce apoptotic cell death. Dimethoxyquinazoline compounds WHI-P131 and WHI-P154 inhibit tyrosine kinase JAK3 in leukemia cells. Of particular interest is WHI-P131, which inhibits JAK3 but not JAK1, JAK2, SYK, BTK, LYN, or IRK at concentrations as high as 350 microm. Studies of BTK inhibitors showed that the leflunomide metabolite analog LFM-A13 inhibited BTK in leukemia and lymphoma cells. Consistent with the anti-apoptotic function of BTK, treatment of leukemic cells with LFM-A13 enhanced their sensitivity to chemotherapy-induced apoptosis.

ACCESSION NUMBER: 2002469935 MEDLINE

DOCUMENT NUMBER: 22176495 PubMed ID: 12188892

TITLE: Structure-based design of novel anticancer agents.

AUTHOR: Uckun F M; Sudbeck E A; Mao C; Ghosh S; Liu X P; Vassilev A O; Navara C S; Narla R K

CORPORATE SOURCE: Drug Discovery Program, Parker Hughes Cancer Center, Parker Hughes Institute, 2665 Long Lake Road, St. Paul, Minnesota 55113, USA.. Fatih.Uckun@ih.org

SOURCE: Curr Cancer Drug Targets, (2001 May) 1 (1) 59-71. Ref: 123  
Journal code: 101094211. ISSN: 1568-0096.

PUB. COUNTRY: Netherlands

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
General Review; (REVIEW)  
(REVIEW, ACADEMIC)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200210

ENTRY DATE: Entered STN: 20020917

Last Updated on STN: 20021002

Entered Medline: 20021001

L1 ANSWER 5 OF 52 MEDLINE

TI The common gamma chain (gamma c) is a required signaling component of the IL-21 receptor and supports IL-21-induced cell proliferation via JAK3.

AB The common cytokine receptor gamma chain (gamma c), an essential component of the receptors for IL-2, IL-4, IL-7, IL-9, and IL-15, is critical for the development and function of lymphocytes. Recently, a novel lymphokine (IL-21) and its receptor (IL-21R alpha) were described which profoundly



affect the growth and activation state of B, T, and NK cells in concert with other lymphokines or stimuli [Parrish-Novak, J., et al. (2000) Nature 408, 57-63]. In this report, we show that gamma c is also a required signaling component of the IL-21 receptor (IL-21R) using the gamma c-deficient X-linked severe combined immunodeficiency (XSCID) lymphoblastoid cell line JT, and JT cells reconstituted with gamma c (JT/gamma c). Moreover, we demonstrate a functional requirement for both gamma c and the gamma c-associated Janus family tyrosine kinase 3 (JAK3) in IL-21-induced proliferation of pro-B-lymphoid cells engineered to express human IL-21R alpha (BaF3/IL-21R alpha). Retroviral-mediated transduction of wild-type gamma c into XSCID JT cells restored function to the IL-21R, as shown by IL-21-induced tyrosine phosphorylation of JAK1 and JAK3, and downstream activation of STAT5, in JT/gamma c cells as well as BaF3/IL-21R alpha and primary splenic B cells. In contrast, IL-21 failed to activate the JAK-STAT pathway in nonreconstituted JT cells. Monoclonal antibodies specific for the gamma c chain effectively inhibited IL-21-induced growth of BaF3/IL-21R alpha cells, supporting a functional role for this molecule in the IL-21R complex. In addition, the specific JAK3 tyrosine kinase inhibitor WHI-P131 significantly reduced IL-21-induced proliferation of BaF3/IL-21R alpha cells. Taken together, these results definitively demonstrate that IL-21-mediated signaling requires the gamma c chain, and indicate that JAK3 is an essential transducer of gamma c-dependent survival and/or mitogenic signals induced by this cytokine.

ACCESSION NUMBER: 2002372867 MEDLINE  
DOCUMENT NUMBER: 22088156 PubMed ID: 12093291  
TITLE: The common gamma chain (gamma c) is a required signaling component of the IL-21 receptor and supports IL-21-induced cell proliferation via JAK3.  
AUTHOR: Habib Tania; Senadheera Shantha; Weinberg Kenneth; Kaushansky Kenneth  
CORPORATE SOURCE: Division of Hematology, University of Washington School of Medicine, Seattle, Washington 98195, USA.  
CONTRACT NUMBER: P50 HL54850 (NHLBI)  
R01 AI40581 (NIAID)  
R01 AI43745 (NIAID)  
R01 CA31615 (NCI)  
R01 DK49855 (NIDDK)  
SOURCE: BIOCHEMISTRY, (2002 Jul 9) 41 (27) 8725-31.  
Journal code: 0370623. ISSN: 0006-2960.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200208  
ENTRY DATE: Entered STN: 20020717  
Last Updated on STN: 20020822  
Entered Medline: 20020821

L1 ANSWER 6 OF 52 MEDLINE  
TI Janus kinase 3 inhibitor WHI-P131/JANEX-1 prevents graft-versus-host disease but spares the graft-versus-leukemia function of the bone marrow allografts in a murine bone marrow transplantation model.  
AB The purpose of the present study was to evaluate the effects of graft-versus-host disease (GVHD) prophylaxis with the Janus kinase 3 (JAK3) inhibitor WHI-P131/JANEX-1 on the graft-versus-leukemic (GVL) function of marrow allografts in mice undergoing bone marrow transplantation (BMT) after being challenged with an otherwise invariably fatal dose of BCL-1 leukemia cells. GVHD prophylaxis using WHI-P131 markedly improved the survival outcome after BMT. The probability of survival at 30 days after BMT was 11% +/- 6% for vehicle-treated recipients (median survival time; 25 days) versus 63% +/- 12% for recipients treated with WHI-P131 (median survival time, 36 days; P <.0001). Because

WHI-P131 is devoid of antileukemic activity against BCL-1 leukemia cells, this marked improvement in survival outcome was due to reduced incidence of GVHD-associated fatalities combined with sustained GVL function of the allografts in the WHI-P131 group. Notably, adoptive transfer experiments demonstrated that the spleens of WHI-P131-treated allograft recipients contained less than 0.001% BCL-1 cells. Notably, GVHD prophylaxis with WHI-P131 plus methotrexate resulted in 100% survival of mice receiving allotransplants challenged with an otherwise invariably fatal dose of BCL-1 leukemia. Taken together, our results provide strong experimental evidence that GVHD prophylaxis using WHI-P131 does not impair the GVL function of the allografts and consequently contributes to an improved post-BMT survival outcome of the recipient mice.

ACCESSION NUMBER: 2002271117 MEDLINE  
DOCUMENT NUMBER: 22005998 PubMed ID: 12010825  
TITLE: Janus kinase 3 inhibitor WHI-P131  
/JANEX-1 prevents graft-versus-host disease but spares the graft-versus-leukemia function of the bone marrow allografts in a murine bone marrow transplantation model.  
AUTHOR: Uckun Fatih M; Roers Bertram A; Waurzyniak Barbara; Liu Xing-Ping; Cetkovic-Cvrlje Marina  
CORPORATE SOURCE: Experimental BMT Program, Parker Hughes Cancer Center and Department of Immunology, Parker Hughes Institute, St Paul, MN 55113, USA.. faith\_uckun@ih.org  
SOURCE: BLOOD, (2002 Jun 1) 99 (11) 4192-9.  
Journal code: 7603509. ISSN: 0006-4971.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals  
ENTRY MONTH: 200207  
ENTRY DATE: Entered STN: 20020516  
Last Updated on STN: 20020702  
Entered Medline: 20020701

L1 ANSWER 7 OF 52 MEDLINE  
TI CYP1A-mediated metabolism of the Janus kinase-3 inhibitor 4-(4'-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline: structural basis for inactivation by regioselective O-demethylation.  
AB Here we report the phase I metabolism of the rationally designed Janus kinase-3 (JAK) inhibitor 4-(4'-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline (WHI-P131; JANEX-1). JANEX-1 was metabolized by the cytochrome P450 enzymes CYP1A1 and CYP1A2 in a regioselective fashion to form the biologically inactive 7-O-demethylation product 4-(4'-hydroxyphenyl)-amino-6-methoxy-7-hydroxyquinazoline (JANEX-1-M). Our molecular modeling studies indicated that the CYP1A family enzymes bind and demethylate JANEX-1 at the C-7 position of the quinazoline ring since the alternative binding conformation with demethylation at the C-6 position would result in a severe steric clash with the binding site residues. The metabolism of JANEX-1 to JANEX-1-M in pooled human liver microsomes followed Michaelis-Menten kinetics with V(max) and K(m) values (mean +/- S.D.) of 34.6 +/- 9.8 pmol/min/mg and 107.3 +/- 66.3 microm, respectively. alpha-Naphthoflavone and furafylline, which both inhibit CYP1A2, significantly inhibited the formation of JANEX-1-M in human liver microsomes. There was a direct correlation between CYP1A activities and the magnitude of JANEX-1-M formation in the liver microsomes from different animal species. A significantly increased metabolic rate for JANEX-1 was observed in Aroclor 1254-, beta-naphthoflavone-, and 3-methylcholanthrene-induced microsomes but not in clofibrate-, dexamethasone-, isoniazid-, and phenobarbital-induced microsomes. The formation of JANEX-1-M in the presence of baculovirus-expressed CYP1A1 and 1A2 was consistent with Michaelis-Menten kinetics. The systemic clearance of JANEX-1-M was much faster than that of JANEX-1 (5525.1 +/- 1926.2 ml/h/kg versus 1458.0 +/- 258.6 ml/h/kg).

Consequently, the area under the curve value for JANEX-1-M was much smaller than that for JANEX-1 (27.5 +/- 8.0 versus 94.8 +/- 18.4 microm. h; P < 0.001).

ACCESSION NUMBER: 2002046792 MEDLINE  
DOCUMENT NUMBER: 21610538 PubMed ID: 11744615  
TITLE: CYP1A-mediated metabolism of the Janus kinase-3 inhibitor 4-(4'-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline: structural basis for inactivation by regioselective O-demethylation.  
AUTHOR: Uckun Fatih M; Thoen Jason; Chen Hao; Sudbeck Elise; Mao Chen; Malaviya Ravi; Liu Xing-Ping; Chen Chun-Lin  
CORPORATE SOURCE: Department of Pharmaceutical Sciences, Parker Hughes Cancer Center, 2665 Long Lake Road, Suite 330, St. Paul, MN 55113, USA.. fatih\_uckun@ih.org  
SOURCE: DRUG METABOLISM AND DISPOSITION, (2002 Jan) 30 (1) 74-85. Journal code: 9421550. ISSN: 0090-9556.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200202  
ENTRY DATE: Entered STN: 20020125  
Last Updated on STN: 20020207  
Entered Medline: 20020206

L1 ANSWER 8 OF 52 MEDLINE  
TI Targeting Janus kinase 3 to attenuate the severity of acute graft-versus-host disease across the major histocompatibility barrier in mice.  
AB To prevent the development of acute graft-versus-host disease (GVHD) in lethally irradiated C57BL/6 (H-2b) recipient mice transplanted with bone marrow-splenocyte grafts from major histocompatibility complex (MHC) disparate BALB/c mice (H-2d), recipient mice were treated with the rationally designed JAK3 inhibitor WHI-P131 [4-(4'-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline] (20 mg/kg, 3 times a day [tid]) daily from the day of bone marrow transplantation (BMT) until the end of the 85-day observation period. Total body irradiation (TBI)-conditioned, vehicle-treated control C57BL/6 mice (n = 38) receiving bone marrow-splenocyte grafts from BALB/c mice survived acute TBI toxicity, but they all developed histologically confirmed severe multi-organ GVHD and died after a median survival time of 37 days. WHI-P131 treatment (20 mg/kg intraperitoneally, tid) prolonged the median survival time of the BMT recipients to 56 days. The probability of survival at 2 months after BMT was 11% +/- 5% for vehicle-treated control mice (n = 38) and 41% +/- 9% for mice treated with WHI-P131 (n = 32) (P < .0001). Notably, the combination regimen WHI-P131 plus the standard anti-GVHD drug methotrexate (MTX) (10 mg/m2 per day) was more effective than WHI-P131 or MTX alone. More than half the C57BL/6 recipients receiving this most effective GVHD prophylaxis remained alive and healthy throughout the 85-day observation period, with a cumulative survival probability of 70% +/- 10%. Taken together, these results indicate that targeting JAK3 in alloreactive donor lymphocytes with a chemical inhibitor such as WHI-P131 may attenuate the severity of GVHD after BMT.

ACCESSION NUMBER: 2001477024 MEDLINE  
DOCUMENT NUMBER: 21411481 PubMed ID: 11520814  
TITLE: Targeting Janus kinase 3 to attenuate the severity of acute graft-versus-host disease across the major histocompatibility barrier in mice.  
AUTHOR: Cetkovic-Cvrlje M; Roers B A; Waurzyniak B; Liu X P; Uckun F M  
CORPORATE SOURCE: Experimental BMT Program, Parker Hughes Cancer Center, and the Department of Immunology, Parker Hughes Institute, St

SOURCE: Paul, MN 55113, USA.  
BLOOD, (2001 Sep 1) 98 (5) 1607-13.  
Journal code: 7603509. ISSN: 0006-4971.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals  
ENTRY MONTH: 200110  
ENTRY DATE: Entered STN: 20010827  
Last Updated on STN: 20011008  
Entered Medline: 20011004

L1 ANSWER 9 OF 52 MEDLINE

TI Role of a JAK3-dependent biochemical signaling pathway in platelet activation and aggregation.

AB Here we provide experimental evidence that identifies JAK3 as one of the regulators of platelet function. Treatment of platelets with thrombin induced tyrosine phosphorylation of the JAK3 target substrates STAT1 and STAT3. Platelets from JAK3-deficient mice displayed a decrease in tyrosine phosphorylation of STAT1 and STAT3. In accordance with these data, pretreatment of human platelets with the JAK3 inhibitor WHI-P131 markedly decreased the base-line enzymatic activity of constitutively active JAK3 and abolished the thrombin-induced tyrosine phosphorylation of STAT1 and STAT3. Following thrombin stimulation, WHI-P131-treated platelets did not undergo shape changes indicative of activation such as pseudopod formation. WHI-P131 inhibited thrombin-induced degranulation/serotonin release as well as platelet aggregation. Highly effective platelet inhibitory plasma concentrations of WHI-P131 were achieved in mice without toxicity. WHI-P131 prolonged the bleeding time of mice in a dose-dependent manner and improved event-free survival in a mouse model of thromboplastin-induced generalized and invariably fatal thromboembolism. To our knowledge, WHI-P131 is the first anti-thrombotic agent that prevents platelet aggregation by inhibiting JAK3.

ACCESSION NUMBER: 2001276171 MEDLINE  
DOCUMENT NUMBER: 21264561 PubMed ID: 11278899  
TITLE: Role of a JAK3-dependent biochemical signaling pathway in platelet activation and aggregation.  
AUTHOR: Tibbles H E; Vassilev A; Wendorf H; Schonhoff D; Zhu D; Lorenz D; Waurzyniak B; Liu X P; Uckun F M  
CORPORATE SOURCE: Parker Hughes Cancer Center, Departments of Hematology, Parker Hughes Institute, St. Paul, Minnesota, 55113, USA.  
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2001 May 25) 276 (21) 17815-22.  
Journal code: 2985121R. ISSN: 0021-9258.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200107  
ENTRY DATE: Entered STN: 20010709  
Last Updated on STN: 20030105  
Entered Medline: 20010705

L1 ANSWER 10 OF 52 MEDLINE

TI In vivo pharmacokinetics and anti-anaphylactic activity of the novel mast cell inhibitor 4-(4'-hydroxylphenyl)-amino-6,7-dimethoxyquinazoline (WHI-P131).

AB WHI-P131 is a novel dimethoxyquinazoline compound that is a potent inhibitor of Janus kinase-3-(JAK3)-dependent mast cell responses. In the present study, the authors investigated the anti-anaphylactic activity and pharmacokinetics of WHI-P131 in mice. After intraperitoneal (i.p.) administration of two

consecutive bolus doses of 25 mg/kg injected 30 min apart at dose level of 25 mg/kg, **WHI-P131** was rapidly absorbed with an observed C(max) of 82.6 microM, which is higher than the target concentration of 30 microM, at which **WHI-P131** abrogates mast cell responses in vitro and the time to reach the maximum plasma concentration (t(max)) was 10.0+/-2.9 min. At a nontoxic 50 mg/kg dose level, **WHI-P131** prevented compound 48/80-induced mast cell histamine release and fatal anaphylaxis in mice. Further development of **WHI-P131** may provide the basis for new and effective treatment as well as prevention programs for mast cell mediated allergic reactions in clinical settings.

ACCESSION NUMBER: 2001265090 MEDLINE  
DOCUMENT NUMBER: 21201516 PubMed ID: 11304656  
TITLE: In vivo pharmacokinetics and anti-anaphylactic activity of the novel mast cell inhibitor 4-(4'-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline (**WHI-P131**).  
AUTHOR: Malavija R; Chen C L; Liu X P; Uckun F M  
CORPORATE SOURCE: Department of Allergy, Parker Hughes Institute, St. Paul, MN, USA.  
SOURCE: AMERICAN JOURNAL OF THERAPEUTICS, (2001 Jan-Feb) 8 (1) 35-9.  
Journal code: 9441347. ISSN: 1075-2765.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200105  
ENTRY DATE: Entered STN: 20010604  
Last Updated on STN: 20010604  
Entered Medline: 20010531

=> d his

(FILE 'HOME' ENTERED AT 13:19:41 ON 08 MAY 2003)

FILE 'WPIDS, MEDLINE, BIOSIS, DGENE, EMBASE, JAPIO, FSTA, JICST-EPLUS'  
ENTERED AT 13:21:46 ON 08 MAY 2003

L1 52 S WHI-P131  
L2 11 S JAK-3 INHIBITORS  
L3 73225 S GRAFT VERSUS HOST DISEASE

=> d l1 ti abs ibib 11-52

L1 ANSWER 11 OF 52 MEDLINE  
TI An inhibitor of Janus kinase 3:4-(4-hydroxyphenylamino)-6,7-dimethoxyquinazolin-1-ium chloride methanol solvate.  
AB The crystal structure of the title compound, C(16)H(16)N(3)O(3)(+). Cl(-).CH(4)O (**WHI-P131**, an inhibitor of Janus kinase 3), contains four hydrogen bonds. There are two hydrogen bonds within the asymmetric unit, i.e. interactions between **WHI-P131** OH and Cl(-), and between methanol and Cl(-). There is a third interaction between **WHI-P131** NH and Cl(-) (related by a 2(1) screw) and a fourth between **WHI-P131** NH and methanol (related by an n-glide). The hydrogen-bond pattern for these interactions can be described by the first-level hydrogen-bond graph-set notation D(1)(1)(2)D(1)(1)(2)D(1)(1)(2)D(1)(1)(2). The second-level graph-set notation (for combinations of two hydrogen bonds) was determined to be D(1)(2)(3)D(1)(2)(3)D(2)(2)(4)D(2)(2)(9)D(2)(2)(14)C(1)(2)(9).

ACCESSION NUMBER: 2001081058 MEDLINE  
DOCUMENT NUMBER: 20480253 PubMed ID: 11025327  
TITLE: An inhibitor of Janus kinase 3:4-(4-hydroxyphenylamino)-6,7-dimethoxyquinazolin-1-ium chloride methanol solvate.  
AUTHOR: Sudbeck E A; Jennissen J D; Liu X P; Uckun F M

CORPORATE SOURCE: Drug Discovery Program, Parker Hughes Institute, 2665 Long Lake Road, Suite 330, St Paul, Minnesota, USA..  
 esudbeck@ih.org  
 SOURCE: ACTA CRYSTALLOGRAPHICA. SECTION C, CRYSTAL STRUCTURE COMMUNICATIONS, (2000 Oct) 56 ( Pt 10) 1282-3.  
 Journal code: 8305826. ISSN: 0108-2701.  
 PUB. COUNTRY: Denmark  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200101  
 ENTRY DATE: Entered STN: 20010322  
 Last Updated on STN: 20010322  
 Entered Medline: 20010105

L1 ANSWER 12 OF 52 MEDLINE

TI A specific inhibitor of janus kinase-3 increases survival in a transgenic mouse model of amyotrophic lateral sclerosis.

AB Amyotrophic lateral sclerosis (ALS) is a progressive, fatal neurodegenerative disorder involving the motor neurons of cortex, brain stem, and spinal cord. About 10% of all ALS patients are familial cases (FALS), of which 20% have mutations in the Cu, Zn-superoxide dismutase (SOD1) gene. The murine model for FALS, which overexpresses a FALS variant of the SOD1 gene, exhibits progressive limbic paralysis followed by death. Treatment of FALS mice with WHI-P131, a specific inhibitor of Janus kinase 3 (JAK3), increased survival by more than two months, suggesting that specific inhibitors of JAK3 may be useful in the treatment of human ALS. These results uniquely establish JAK3 as a novel molecular target for the treatment of FALS.  
 Copyright 2000 Academic Press.

ACCESSION NUMBER: 2000090586 MEDLINE  
 DOCUMENT NUMBER: 20090586 PubMed ID: 10623568  
 TITLE: A specific inhibitor of janus kinase-3 increases survival in a transgenic mouse model of amyotrophic lateral sclerosis.  
 AUTHOR: Trieu V N; Liu R; Liu X P; Uckun F M  
 CORPORATE SOURCE: Drug Discovery Program, Department of Neurosciences, Hughes Institute, 2665 Long Lake Road, Roseville, Minnesota, 55113, USA..  
 SOURCE: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (2000 Jan 7) 267 (1) 22-5.  
 Journal code: 0372516. ISSN: 0006-291X.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200002  
 ENTRY DATE: Entered STN: 20000218  
 Last Updated on STN: 20000218  
 Entered Medline: 20000208

L1 ANSWER 13 OF 52 MEDLINE

TI In vivo toxicity and pharmacokinetic features of the janus kinase 3 inhibitor WHI-P131 [4-(4'-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline.

AB 4-(4'-Hydroxyphenyl)-amino-6,7-dimethoxyquinazoline (WHI-P131) is a potent and selective inhibitor of the Janus kinase 3, which triggers apoptosis in human acute lymphoblastic leukemia (ALL) cells. In this preclinical study, we evaluated the pharmacokinetics and toxicity of WHI-P131 in rats, mice, and cynomolgus monkeys. Following i.v. administration, the terminal elimination half-life of WHI-P131 was 73.2 min in rats, 103.4 min in mice, and 45.0 min in monkeys. The i.v. administered WHI-P131 showed a very wide tissue distribution in mice. Following

i.p. administration, **WHI-P131** was rapidly absorbed in both rats and mice, and the time to reach the maximum plasma concentration (tmax) was 24.8 min in rats and 10.0 min in mice. Subsequently, **WHI-P131** was eliminated with a terminal elimination half-life of 51.8 min in rats and 123.6 min in mice. The estimated i.p. bioavailability was 95% for rats, as well as for mice. **WHI-P131** was quickly absorbed after oral administration in mice with a tmax of 5.8 min, but its oral bioavailability was relatively low (29.6%). The elimination half-life of **WHI-P131** after oral administration was 297.6 min. **WHI-P131** was not acutely toxic to mice at single i.p. bolus doses ranging from 0.5-250 mg/kg. Two cynomolgus monkeys treated with 20 mg/kg **WHI-P131** and one cynomolgus monkey treated with 100 mg/kg **WHI-P131** experienced no side effects. Plasma samples from **WHI-P131**-treated monkeys exhibited potent antileukemic activity against human ALL cells in vitro. To our knowledge, this is the first preclinical toxicity and pharmacokinetic study of a Janus kinase 3 inhibitor. Further development of **WHI-P131** may provide the basis for new and effective treatment programs for relapsed ALL in clinical settings.

ACCESSION NUMBER: 2000005757 MEDLINE  
DOCUMENT NUMBER: 20005757 PubMed ID: 10537365  
TITLE: In vivo toxicity and pharmacokinetic features of the janus kinase 3 inhibitor **WHI-P131** [4-(4'-hydroxyphenyl)-amino-6,7- dimethoxyquinazoline].  
AUTHOR: Uckun F M; Ek O; Liu X P; Chen C L  
CORPORATE SOURCE: Parker Hughes Cancer Center, Department of Oncology, Hughes Institute, St. Paul, Minnesota 55113, USA.  
SOURCE: CLINICAL CANCER RESEARCH, (1999 Oct) 5 (10) 2954-62. Journal code: 9502500. ISSN: 1078-0432.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199911  
ENTRY DATE: Entered STN: 20000111  
Last Updated on STN: 20000111  
Entered Medline: 19991124

L1 ANSWER 14 OF 52 MEDLINE  
TI Targeting Janus kinase 3 in mast cells prevents immediate hypersensitivity reactions and anaphylaxis.  
AB Janus kinase 3 (JAK3), a member of the Janus family protein-tyrosine kinases, is expressed in mast cells, and its enzymatic activity is enhanced by IgE receptor/FcepsilonRI cross-linking. Selective inhibition of JAK3 in mast cells with 4-(4'-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline (**WHI-P131**) blocked the phospholipase C activation, calcium mobilization, and activation of microtubule-associated protein kinase after IgE receptor/FcepsilonRI cross-linking. Treatment of IgE-sensitized rodent as well as human mast cells with **WHI-P131** effectively inhibited the activation-associated morphological changes, degranulation, and proinflammatory mediator release after specific antigen challenge without affecting the functional integrity of the distal secretory machinery. In vivo administration of the JAK3 inhibitor **WHI-P131** prevented mast cell degranulation and development of cutaneous as well as systemic fatal anaphylaxis in mice at nontoxic dose levels. Thus, JAK3 plays a pivotal role in IgE receptor/FcepsilonRI-mediated mast cell responses, and targeting JAK3 with a specific inhibitor, such as **WHI-P131**, may provide the basis for new and effective treatment as well as prevention programs for mast cell-mediated allergic reactions.

ACCESSION NUMBER: 1999410442 MEDLINE  
DOCUMENT NUMBER: 99410442 PubMed ID: 10480916

TITLE: Targeting Janus kinase 3 in mast cells prevents immediate hypersensitivity reactions and anaphylaxis.  
 COMMENT: Erratum in: J Biol Chem 1999 Dec 31;274(53):38276  
 AUTHOR: Malaviya R; Zhu D; Dibirdik I; Uckun F M  
 CORPORATE SOURCE: Department of Allergy, Hughes Institute, St. Paul, Minnesota 55113, USA.  
 SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1999 Sep 17) 274 (38) 27028-38.  
 Journal code: 2985121R. ISSN: 0021-9258.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199910  
 ENTRY DATE: Entered STN: 19991026  
 Last Updated on STN: 20000320  
 Entered Medline: 19991013

L1 ANSWER 15 OF 52 MEDLINE

TI Structure-based design of specific inhibitors of Janus kinase 3 as apoptosis-inducing antileukemic agents.

AB A novel homology model of the kinase domain of Janus kinase (JAK) 3 was used for the structure-based design of dimethoxyquinazoline compounds with potent and specific inhibitory activity against JAK3. The active site of JAK3 in this homology model measures roughly 8 Å x 11 Å x 20 Å, with a volume of approximately 530 Å<sup>3</sup> available for inhibitor binding. Modeling studies indicated that 4-(phenyl)-amino-6,7-dimethoxyquinazoline (parent compound WHI-258) would likely fit into the catalytic site of JAK3 and that derivatives of this compound that contain an OH group at the 4' position of the phenyl ring would more strongly bind to JAK3 because of added interactions with Asp-967, a key residue in the catalytic site of JAK3. These predictions were consistent with docking studies indicating that compounds containing a 4'-OH-group, **WHI-P131** [4-(4'-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline], WHI-P154 [4-(3'-bromo-4'-hydroxylphenyl)-amino-6,7-dimethoxyquinazoline], and WHI-P97 [4-(3',5'-dibromo-4'-hydroxylphenyl)-amino-6,7-dimethoxyquinazoline], were likely to bind favorably to JAK3, with estimated K(i)s ranging from 0.6 to 2.3 microm. These compounds inhibited JAK3 in immune complex kinase assays in a dose-dependent fashion. In contrast, compounds lacking the 4'-OH group, WHI-P79 [4-(3'-bromophenyl)-amino-6,7-dimethoxyquinazoline], WHI-P111 [4-(3'-bromo-4'-methylphenyl)-amino-6,7-dimethoxyquinazoline], WHI-P112 [4-(2',5'-dibromophenyl)-amino-6,7-dimethoxyquinazoline], WHI-P132 [4-(2'-hydroxylphenyl)-amino-6,7-dimethoxyquinazoline], and WHI-P258 [4-(phenyl)-amino-6,7-dimethoxyquinazoline], were predicted to bind less strongly, with estimated K(i)s ranging from 28 to 72 microm. These compounds did not show any significant JAK3 inhibition in kinase assays. Furthermore, the lead dimethoxyquinazoline compound, **WHI-P131**, which showed potent JAK3-inhibitory activity (IC<sub>50</sub> of 78 microm), did not inhibit JAK1 and JAK2, the ZAP/SYK family tyrosine kinase SYK, the TEC family tyrosine kinase BTK, the SRC family tyrosine kinase LYN, or the receptor family tyrosine kinase insulin receptor kinase, even at concentrations as high as 350 microm. **WHI-P131** induced apoptosis in JAK3-expressing human leukemia cell lines NALM-6 and LCL19 but not in melanoma (M24-MET) or squamous carcinoma (SQ20B) cells. Leukemia cells were not killed by dimethoxyquinazoline compounds that were inactive against JAK3. **WHI-P131** inhibited the clonogenic growth of JAK3-positive leukemia cell lines DAUDI, RAMOS, LCL19, NALM-6, MOLT-3, and HL-60 (but not JAK3-negative BT-20 breast cancer, M24-MET melanoma, or SQ20B squamous carcinoma cell lines) in a concentration-dependent fashion. Potent and specific inhibitors of JAK3 such as **WHI-P131** may provide the basis for the design of new treatment strategies against acute lymphoblastic leukemia, the most common form of childhood cancer.



ACCESSION NUMBER: 1999316808 MEDLINE  
DOCUMENT NUMBER: 99316808 PubMed ID: 10389946  
TITLE: Structure-based design of specific inhibitors of Janus  
kinase 3 as apoptosis-inducing antileukemic agents.  
AUTHOR: Sudbeck E A; Liu X P; Narla R K; Mahajan S; Ghosh S; Mao C;  
Uckun F M  
CORPORATE SOURCE: Department of Structural Biology, Hughes Institute, St.  
Paul, Minnesota 55113, USA.  
SOURCE: CLINICAL CANCER RESEARCH, (1999 Jun) 5 (6) 1569-82.  
Journal code: 9502500. ISSN: 1078-0432.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199909  
ENTRY DATE: Entered STN: 19991012  
Last Updated on STN: 19991012  
Entered Medline: 19990930

L1 ANSWER 16 OF 52 MEDLINE

TI Quantitative high-performance liquid chromatographic method for  
pharmacokinetic studies of the potent mast cell inhibitor  
4-(4'-hydroxyphenyl)amino-6,7-dimethoxyquinazoline (WHI-  
P131).

AB The novel quinazoline derivative 4-(4'-hydroxyphenyl)amino-6,7-  
dimethoxyquinazoline (WHI-P131) has recently been  
identified as a potent mast cell inhibitor capable of preventing  
IgE/antigen induced cutaneous as well as systemic fatal anaphylaxis in  
mice. Here we describe a sensitive high-performance liquid chromatography  
(HPLC)-based quantitative detection method for measurement of WHI  
-P131 levels in plasma as well as in target mast cells. The  
average extraction recovery for WHI-P131 was 88.4% for  
plasma and 75.7% for RBL-2H3 mast cell lysates. Good linearity ( $r > 0.999$ )  
was observed throughout the concentration range of 0.1-20 microm in plasma  
and 0.01-5 nmol in  $5 \times 10^6$  cells (0.5-238 microm per cell) for  
WHI-P131. Intra- and inter-assay variabilities were  $< 7\%$   
and the lowest detection limit of WHI-P131 was 0.05  
microm in plasma and 0.005 nmol in 5 million cells, respectively, at a  
signal-to-noise ratio of approximately 2. The practical utility of this  
new HPLC method was confirmed in a pilot pharmacokinetic study in BALB/c  
mice as well as in a cellular drug uptake and disposition study in RBL-2H3  
mast cells. After intraperitoneal administration of a non-toxic 40 mg/kg  
bolus dose of WHI-P131, the estimated maximum plasma  
concentration was 92.7 microm, which is approximately 1-log higher than  
the effective in vitro mast cell inhibitory concentrations of WHI  
-P131. The drug absorption was rapid with an absorption  
half-life of only 2.9 min and the estimated time to reach the maximum  
plasma concentration was 8.3 min. WHI-P131 was  
cleared with an apparent systemic clearance rate of 2586 ml/h/kg and an  
elimination half-life of 1.8 h. An intracellular exposure level (AUC) of  
55 microm x h was obtained after in vitro treatment of RBL-2H3 mast cells  
with WHI-P131 at a 33.6 microm final concentration in  
culture medium. The availability of the described quantitative HPLC  
detection method for WHI-P131 provides the basis for  
further development of WHI-P131 as an anti-allergic  
drug through detailed pharmacodynamic studies in preclinical animal  
models.

ACCESSION NUMBER: 1999287184 MEDLINE  
DOCUMENT NUMBER: 99287184 PubMed ID: 10360439  
TITLE: Quantitative high-performance liquid chromatographic method  
for pharmacokinetic studies of the potent mast cell  
inhibitor 4-(4'-hydroxyphenyl)amino-6,7-  
dimethoxyquinazoline (WHI-P131).  
AUTHOR: Chen C L; Malaviya R; Chen H; Liu X P; Uckun F M

CORPORATE SOURCE: Department of Pharmaceutical Sciences, Hughes Institute,  
St. Paul, MN 55113, USA.  
SOURCE: JOURNAL OF CHROMATOGRAPHY. B, BIOMEDICAL SCIENCES AND  
APPLICATIONS, (1999 Apr 30) 727 (1-2) 205-12.  
Journal code: 9714109. ISSN: 1387-2273.  
PUB. COUNTRY: Netherlands  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199907  
ENTRY DATE: Entered STN: 19990730  
Last Updated on STN: 19990730  
Entered Medline: 19990720

L1 ANSWER 17 OF 52 MEDLINE

TI Inhibition of human glioblastoma cell adhesion and invasion by  
4-(4'-hydroxylphenyl)-amino-6,7-dimethoxyquinazoline (WHI-  
P131) and 4-(3'-bromo-4'-hydroxylphenyl)-amino-6,7-  
dimethoxyquinazoline (WHI-P154).

AB Glioblastoma multiforme is a highly invasive primary brain tumor with a  
disappointingly high local recurrence rate and mortality despite intensive  
multimodality treatment programs. Therefore, new agents that are capable  
of inhibiting the infiltration of normal brain parenchyma by glioblastoma  
cells are urgently needed. Here, we show that the novel quinazoline  
derivatives 4-(4'-hydroxylphenyl)-amino-6,7-dimethoxyquinazoline (  
WHI-P131) and 4-(3'-bromo-4'-hydroxylphenyl)-amino-6,7-  
dimethoxyquinazoline (WHI-P154) are potent inhibitors of glioblastoma cell  
adhesion and migration. Specifically, both compounds inhibited at  
micromolar concentrations: (a) integrin-mediated glioblastoma cell  
adhesion to the extracellular matrix proteins laminin, type IV collagen,  
and fibronectin; (b) integrin-independent epidermal growth factor-induced  
adhesion of glioblastoma cells to poly-L-lysine-coated tissue culture  
plates; (c) fetal bovine serum-induced polymerization of actin and actin  
stress fiber formation as well epidermal growth factor-stimulated  
formation of focal adhesion plaques in serum-starved glioblastoma cells;  
and most importantly, (d) glioblastoma cell migration in in vitro assays  
of tumor cell invasiveness using tumor cell spheroids and/or  
Matrigel-coated Boyden chambers. Further preclinical development of  
WHI-P131 and WHI-P154 may provide the basis for the  
design of more effective adjuvant chemotherapy programs for glioblastoma  
multiforme.

ACCESSION NUMBER: 1999011003 MEDLINE

DOCUMENT NUMBER: 99011003 PubMed ID: 9796979

TITLE: Inhibition of human glioblastoma cell adhesion and invasion  
by 4-(4'-hydroxylphenyl)-amino-6,7-dimethoxyquinazoline (  
WHI-P131) and 4-(3'-bromo-4'-  
hydroxylphenyl)-amino-6,7-dimethoxyquinazoline (WHI-P154).

AUTHOR: Narla R K; Liu X P; Klis D; Uckun F M

CORPORATE SOURCE: Department of Experimental Oncology, and Wayne Hughes  
Institute, St. Paul, Minnesota 55113, USA.

SOURCE: CLINICAL CANCER RESEARCH, (1998 Oct) 4 (10) 2463-71.  
Journal code: 9502500. ISSN: 1078-0432.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199812

ENTRY DATE: Entered STN: 19990115

Last Updated on STN: 20000303

Entered Medline: 19981229

L1 ANSWER 18 OF 52 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

TI Structure-based design of novel anticancer agents.

ACCESSION NUMBER: 2003:36580 BIOSIS

DOCUMENT NUMBER: PREV200300036580  
TITLE: Structure-based design of novel anticancer agents.  
AUTHOR(S): Uckun, F. M. (1); Sudbeck, E. A.; Mao, C.; Ghosh, S.; Liu, X.-P.; Vassilev, A. O.; Navara, C. S.; Narla, R. K.  
CORPORATE SOURCE: (1) Hughes Chair in Oncology, Drug Discovery Program, Parker Hughes Cancer Center, Parker Hughes Institute, 2665 Long Lake Road, Saint Paul, MN, 55113, USA: Fatih\_Uckun@ih.org USA  
SOURCE: Current Cancer Drug Targets, (May 2001, 2001) Vol. 1, No. 1, pp. 59-71. print.  
ISSN: 1568-0096.  
DOCUMENT TYPE: General Review  
LANGUAGE: English

L1 ANSWER 19 OF 52 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.  
TI The MAPK and JAK3 signaling pathways in mastocytosis.  
ACCESSION NUMBER: 2002:494839 BIOSIS  
DOCUMENT NUMBER: PREV200200494839  
TITLE: The MAPK and JAK3 signaling pathways in mastocytosis.  
AUTHOR(S): Chan, I. (1); Kayashima, K.; Tharp, M. (1)  
CORPORATE SOURCE: (1) Department of Dermatology, Rush-Presbyterian-St. Luke, Chicago, IL USA  
SOURCE: Journal of Investigative Dermatology, (July, 2002) Vol. 119, No. 1, pp. 282. <http://www.jidonline.org>. print.  
Meeting Info.: 63rd Annual Meeting of the Society for Investigative Dermatology Los Angeles, California, USA May 15-18, 2002  
ISSN: 0022-202X.  
DOCUMENT TYPE: Conference  
LANGUAGE: English

L1 ANSWER 20 OF 52 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.  
TI The common gamma chain (gammac) is a required signaling component of the IL-21 receptor and supports IL-21-induced cell proliferation via JAK3.  
AB The common cytokine receptor gamma chain (gammac), an essential component of the receptors for IL-2, IL-4, IL-7, IL-9, and IL-15, is critical for the development and function of lymphocytes. Recently, a novel lymphokine (IL-21) and its receptor (IL-21Ralpha) were described which profoundly affect the growth and activation state of B, T, and NK cells in concert with other lymphokines or stimuli (Parrish-Novak, J., et al. (2000) Nature 408, 57-63). In this report, we show that gammac is also a required signaling component of the IL-21 receptor (IL-21R) using the gammac-deficient X-linked severe combined immunodeficiency (XSCID) lymphoblastoid cell line JT, and JT cells reconstituted with gammac (JT/gammac). Moreover, we demonstrate a functional requirement for both gammac and the gammac-associated Janus family tyrosine kinase 3 (JAK3) in IL-21-induced proliferation of pro-B-lymphoid cells engineered to express human IL-21Ralpha (BaF3/IL-21Ralpha). Retroviral-mediated transduction of wild-type gammac into XSCID JT cells restored function to the IL-21R, as shown by IL-21-induced tyrosine phosphorylation of JAK1 and JAK3, and downstream activation of STAT5, in JT/gammac cells as well as BaF3/IL-21Ralpha and primary splenic B cells. In contrast, IL-21 failed to activate the JAK-STAT pathway in nonreconstituted JT cells. Monoclonal antibodies specific for the gammac chain effectively inhibited IL-21-induced growth of BaF3/IL-21Ralpha cells, supporting a functional role for this molecule in the IL-21R complex. In addition, the specific JAK3 tyrosine kinase inhibitor WHI-P131 significantly reduced IL-21-induced proliferation of BaF3/IL-21Ralpha cells. Taken together, these results definitively demonstrate that IL-21-mediated signaling requires the gammac chain, and indicate that JAK3 is an essential transducer of gammac-dependent survival and/or mitogenic signals induced by this cytokine.  
ACCESSION NUMBER: 2002:436913 BIOSIS  
DOCUMENT NUMBER: PREV200200436913

TITLE: The common gamma chain (gammac) is a required signaling component of the IL-21 receptor and supports IL-21-induced cell proliferation via JAK3.  
AUTHOR(S): Habib, Tania; Senadheera, Shantha; Weinberg, Kenneth; Kaushansky, Kenneth (1)  
CORPORATE SOURCE: (1) Department of Medicine, UCSD Medical School, 402 Dickenson St., Suite 380, San Diego, CA, 92103-8811: kkaushansky@ucsd.edu USA  
SOURCE: Biochemistry, (July 9, 2002) Vol. 41, No. 27, pp. 8725-8731. <http://pubs.acs.org/journals/bichaw/>. print. ISSN: 0006-2960.  
DOCUMENT TYPE: Article  
LANGUAGE: English

L1 ANSWER 21 OF 52 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.  
TI Janus kinase 3 inhibitor WHI-P131/JANEX-1 prevents graft-versus-host disease but spares the graft-versus-leukemia function of the bone marrow allografts in a murine bone marrow transplantation model.  
AB The purpose of the present study was to evaluate the effects of graft-versus-host disease (GVHD) prophylaxis with the Janus kinase 3 (JAK3) inhibitor WHI-P131/JANEX-1 on the graft-versus-leukemic (GVL) function of marrow allografts in mice undergoing bone marrow transplantation (BMT) after being challenged with an otherwise invariably fatal dose of BCL-1 leukemia cells. GVHD prophylaxis using WHI-P131 markedly improved the survival outcome after BMT. The probability of survival at 30 days after BMT was 11% +/- 6% for vehicle-treated recipients (median survival time, 25 days) versus 63% +/- 12% for recipients treated with WHI-P131 (median survival time, 36 days; P < .0001). Because WHI-P131 is devoid of antileukemic activity against BCL-1 leukemia cells, this marked improvement in survival outcome was due to reduced incidence of GVHD-associated fatalities combined with sustained GVL function of the allografts in the WHI-P131 group. Notably, adoptive transfer experiments demonstrated that the spleens of WHI-P131-treated allograft recipients contained less than 0.001% BCL-1 cells. Notably, GVHD prophylaxis with WHI-P131 plus methotrexate resulted in 100% survival of mice receiving allotransplants challenged with an otherwise invariably fatal dose of BCL-1 leukemia. Taken together, our results provide strong experimental evidence that GVHD prophylaxis using WHI-P131 does not impair the GVL function of the allografts and consequently contributes to an improved post-BMT survival outcome of the recipient mice.

ACCESSION NUMBER: 2002:341660 BIOSIS  
DOCUMENT NUMBER: PREV200200341660  
TITLE: Janus kinase 3 inhibitor WHI-P131 /JANEX-1 prevents graft-versus-host disease but spares the graft-versus-leukemia function of the bone marrow allografts in a murine bone marrow transplantation model.  
AUTHOR(S): Uckun, Fatih M. (1); Roers, Bertram A.; Waurzyniak, Barbara; Liu, Xing-Ping; Cetkovic-Cvrlje, Marina  
CORPORATE SOURCE: (1) Parker Hughes Cancer Center, 2665 Long Lake Rd, Suite 300, St Paul, MN, 55113: fatih\_uckun@ih.org USA  
SOURCE: Blood, (June 1, 2002) Vol. 99, No. 11, pp. 4192-4199. <http://www.bloodjournal.org/>. print. ISSN: 0006-4971.  
DOCUMENT TYPE: Article  
LANGUAGE: English

L1 ANSWER 22 OF 52 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.  
TI The interleukin-2 (IL-2) receptor common gamma chain (gammac) is a required signaling component of the IL-21 receptor and supports IL-21-induced cell proliferation via JAK3.  
AB The newly described lymphokines human and murine interleukin-21 (IL-21) are 131 and 122 amino acid polypeptides produced by activated CD4+

lymphocytes. Structurally, IL-21 is most closely related to IL-2 and IL-15, and although IL-21 alone cannot support the proliferation of any subclass of lymphocytes, it profoundly affects the growth and activation state of B-, T and NK cells in concert with other lymphokines or stimuli. The biological effects of IL-21 are mediated through a 538 amino acid class I member of the hematopoietic cytokine receptor superfamily (IL-21Ralpha). Although the complete IL-21R has not yet been defined, IL-21Ralpha is structurally similar to the beta subunit of the receptor for IL-2 and IL-15 (IL-2/15Rbeta) and thus, might utilize the gammac chain for signaling. To test this hypothesis we used the gammac-deficient X-linked severe combined immunodeficiency B cell line JT, and JT cells reconstituted with gammac (JT-gammac). Moreover, we examined the functional requirement of both gammac and the gammac-associated Janus family tyrosine kinase 3 (JAK3) in IL-21-induced proliferation of pro-B-lymphoid cells engineered to express human IL-21Ralpha (BaF3/IL-21Ralpha). Using immunoprecipitation and Western blotting we found that IL-21 stimulated prominent tyrosine phosphorylation (Tyr-P) of JAK1 and JAK3 in BaF3/IL-21Ralpha, primary murine splenic B cells, and JT-gammac. In contrast, IL-21 failed to induce Tyr-P of JAK1 and JAK3 in JT cells. Moreover, STATs 1, 3 and 5 underwent Tyr-P in response to IL-21 in BaF3/IL-21Ralpha-, primary B- and JT-gammac cells but not in JT cells. To determine the functional role of gammac in IL-21 signaling, we conducted MTT proliferation assays with JT-gammac cells and found a specific proliferative response to IL-21; JT cells failed to respond to IL-21. Neutralizing monoclonal antibodies specific for the gammac chain effectively inhibited IL-21-induced growth of BaF3/IL-21Ralpha cells in an MTT assay, further supporting a functional role for this molecule in IL-21R signaling. Finally, the potent and specific JAK3 tyrosine kinase inhibitor **WHI-P131** significantly reduced IL-21-induced proliferation of BaF3/IL-21Ralpha cells relative to the vehicle control. Taken together, these results definitively demonstrate that IL-21-mediated signaling requires the gammac chain of the IL-2 receptor, and indicate that JAK3 is an essential transducer of gammac-dependent survival and/or mitogenic signals induced by this cytokine.

ACCESSION NUMBER: 2002:261534 BIOSIS  
DOCUMENT NUMBER: PREV200200261534  
TITLE: The interleukin-2 (IL-2) receptor common gamma chain (gammac) is a required signaling component of the IL-21 receptor and supports IL-21-induced cell proliferation via JAK3.  
AUTHOR(S): Habib, Tania J. (1); Weinberg, Kenneth I.; Kaushansky, Kenneth (1)  
CORPORATE SOURCE: (1) University of Washington, Seattle, WA USA  
SOURCE: Blood, (November 16, 2001) Vol. 98, No. 11 Part 1, pp. 818a. <http://www.bloodjournal.org/>. print.  
Meeting Info.: 43rd Annual Meeting of the American Society of Hematology, Part 1 Orlando, Florida, USA December 07-11, 2001  
ISSN: 0006-4971.  
DOCUMENT TYPE: Conference  
LANGUAGE: English

L1 ANSWER 23 OF 52 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.  
TI CYP1A-mediated metabolism of the Janus kinase-3 inhibitor 4-(4'-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline: Structural basis for inactivation by regioselective O-demethylation.  
AB Here we report the phase I metabolism of the rationally designed Janus kinase-3 (JAK) inhibitor 4-(4'-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline (**WHI-P131**; JANEX-1). JANEX-1 was metabolized by the cytochrome P450 enzymes CYP1A1 and CYP1A2 in a regioselective fashion to form the biologically inactive 7-O-demethylation product 4-(4'-hydroxyphenyl)-amino-6-methoxy-7-hydroxyquinazoline (JANEX-1-M). Our molecular modeling studies indicated that the CYP1A family enzymes bind and demethylate JANEX-1 at the C-7 position of the

quinazoline ring since the alternative binding conformation with demethylation at the C-6 position would result in a severe steric clash with the binding site residues. The metabolism of JANEX-1 to JANEX-1-M in pooled human liver microsomes followed Michaelis-Menten kinetics with Vmax and Km values (mean  $\pm$  S.D.) of 34.6  $\pm$  9.8 pmol/min/mg and 107.3  $\pm$  66.3  $\mu$ M, respectively.  $\alpha$ -Naphthoflavone and furafylline, which both inhibit CYP1A2, significantly inhibited the formation of JANEX-1-M in human liver microsomes. There was a direct correlation between CYP1A activities and the magnitude of JANEX-1-M formation in the liver microsomes from different animal species. A significantly increased metabolic rate for JANEX-1 was observed in Aroclor 1254-, beta-naphthoflavone-, and 3-methylcholanthrene-induced microsomes but not in clofibrate-, dexamethasone-, isoniazid-, and phenobarbital-induced microsomes. The formation of JANEX-1-M in the presence of baculovirus-expressed CYP1A1 and 1A2 was consistent with Michaelis-Menten kinetics. The systemic clearance of JANEX-1-M was much faster than that of JANEX-1 (5525.1  $\pm$  1926.2 ml/h/kg versus 1458.0  $\pm$  258.6 ml/h/kg). Consequently, the area under the curve value for JANEX-1-M was much smaller than that for JANEX-1 (27.5  $\pm$  8.0 versus 94.8  $\pm$  18.4  $\mu$ M cntdot h;  $P < 0.001$ ).

ACCESSION NUMBER: 2002:101322 BIOSIS  
DOCUMENT NUMBER: PREV200200101322  
TITLE: CYP1A-mediated metabolism of the Janus kinase-3 inhibitor 4-(4'-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline: Structural basis for inactivation by regioselective O-demethylation.  
AUTHOR(S): Uckun, Fatih M. (1); Thoen, Jason; Chen, Hao; Sudbeck, Elise; Mao, Chen; Malaviya, Ravi; Liu, Xing-Ping; Chen, Chun-Lin  
CORPORATE SOURCE: (1) Parker Hughes Cancer Center, 2665 Long Lake Road, Suite 330, St Paul, MN, 55113: fatih\_uckun@ih.org USA  
SOURCE: Drug Metabolism and Disposition, (January, 2002) Vol. 30, No. 1, pp. 74-85. print.  
ISSN: 0090-9556.  
DOCUMENT TYPE: Article  
LANGUAGE: English

L1 ANSWER 24 OF 52 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.  
TI The C-kit signaling pathways in normal and mastocytosis mast cells.  
ACCESSION NUMBER: 2001:483580 BIOSIS  
DOCUMENT NUMBER: PREV200100483580  
TITLE: The C-kit signaling pathways in normal and mastocytosis mast cells.  
AUTHOR(S): Chan, I. (1); Kayashima, K. (1); Ma, Y.; Longley, B.; Tharp, M. (1)  
CORPORATE SOURCE: (1) Dermatology, Rush-Presbyterian-St-Luke's Medical Center, Chicago, IL USA  
SOURCE: Journal of Investigative Dermatology, (August, 2001) Vol. 117, No. 2, pp. 489. print.  
Meeting Info.: 62nd Annual Meeting of the Society for Investigative Dermatology Washington, DC, USA May 09-12, 2001  
ISSN: 0022-202X.  
DOCUMENT TYPE: Conference  
LANGUAGE: English  
SUMMARY LANGUAGE: English

L1 ANSWER 25 OF 52 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.  
TI Islet allograft rejection is prevented by targeting janus kinase 3 (JAK3) with 4-(4'-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline (WHI-P131).  
ACCESSION NUMBER: 2001:479045 BIOSIS  
DOCUMENT NUMBER: PREV200100479045  
TITLE: Islet allograft rejection is prevented by targeting janus

kinase 3 (JAK3) with 4-(4'-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline (WHI-P131).

AUTHOR(S): Cetkovic-Cvrlje, Marina (1); Dragt, Angela L. (1); Olson, Christine M. (1); Uckun, Faith M. (1)  
CORPORATE SOURCE: (1) St. Paul, MN USA  
SOURCE: Diabetes, (June, 2001) Vol. 50, No. Supplement 2, pp. A410. print.  
Meeting Info.: 61st Scientific Sessions of the American Diabetes Association Philadelphia, Pennsylvania, USA June 22-26, 2001  
ISSN: 0012-1797.  
DOCUMENT TYPE: Conference  
LANGUAGE: English  
SUMMARY LANGUAGE: English

L1 ANSWER 26 OF 52 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.  
TI Targeting Janus kinase 3 to attenuate the severity of acute graft-versus-host disease across the major histocompatibility barrier in mice.  
AB To prevent the development of acute graft-versus-host disease (GVHD) in lethally irradiated C57BL/6 (H-2b) recipient mice transplanted with bone marrow-splenocyte grafts from major histocompatibility complex (MHC) disparate BALB/c mice (H-2d), recipient mice were treated with the rationally designed JAK3 inhibitor WHI-P131 (4-(4'-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline) (20 mg/kg, 3 times a day (tid)) daily from the day of bone marrow transplantation (BMT) until the end of the 85-day observation period. Total body irradiation (TBI)-conditioned, vehicle-treated control C57BL/6 mice (n=38) receiving bone marrow-splenocyte grafts from BALB/c mice survived acute TBI toxicity, but they all developed histologically confirmed severe multi-organ GVHD and died after a median survival time of 37 days. WHI-P131 treatment (20 mg/kg intraperitoneally, tid) prolonged the median survival time of the BMT recipients to 56 days. The probability of survival at 2 months after BMT was 11%+-5% for vehicle-treated control mice (n=38) and 41%+-9% for mice treated with WHI-P131 (n=32) (P<.0001). Notably, the combination regimen WHI-P131 plus the standard anti-GVHD drug methotrexate (MTX) (10 mg/m2 per day) was more effective than WHI-P131 or MTX alone. More than half the C57BL/6 recipients receiving this most effective GVHD prophylaxis remained alive and healthy throughout the 85-day observation period, with a cumulative survival probability of 70%+-10%. Taken together, these results indicate that targeting JAK3 in alloreactive donor lymphocytes with a chemical inhibitor such as WHI-P131 may attenuate the severity of GVHD after BMT.

ACCESSION NUMBER: 2001:442093 BIOSIS  
DOCUMENT NUMBER: PREV200100442093  
TITLE: Targeting Janus kinase 3 to attenuate the severity of acute graft-versus-host disease across the major histocompatibility barrier in mice.  
AUTHOR(S): Cetkovic-Cvrlje, Marina; Roers, Bertram A.; Waurzyniak, Barbara; Liu, Xing-Ping; Uckun, Fatih M. (1)  
CORPORATE SOURCE: (1) Parker Hughes Institute, 2665 Long Lake Rd, Ste 300, Saint Paul, MN, 55113: fatih\_uckun@ih.org USA  
SOURCE: Blood, (September 1, 2001) Vol. 98, No. 5, pp. 1607-1613. print.  
ISSN: 0006-4971.  
DOCUMENT TYPE: Article  
LANGUAGE: English  
SUMMARY LANGUAGE: English

L1 ANSWER 27 OF 52 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.  
TI Role of a JAK3-dependent biochemical signaling pathway in platelet activation and aggregation.

AB Here we provide experimental evidence that identifies JAK3 as one of the regulators of platelet function. Treatment of platelets with thrombin induced tyrosine phosphorylation of the JAK3 target substrates STAT1 and STAT3. Platelets from JAK3-deficient mice displayed a decrease in tyrosine phosphorylation of STAT1 and STAT3. In accordance with these data, pretreatment of human platelets with the JAK3 inhibitor **WHI-P131** markedly decreased the base-line enzymatic activity of constitutively active JAK3 and abolished the thrombin-induced tyrosine phosphorylation of STAT1 and STAT3. Following thrombin stimulation, **WHI-P131**-treated platelets did not undergo shape changes indicative of activation such as pseudopod formation. **WHI-P131** inhibited thrombin-induced degranulation/serotonin release as well as platelet aggregation. Highly effective platelet inhibitory plasma concentrations of **WHI-P131** were achieved in mice without toxicity. **WHI-P131** prolonged the bleeding time of mice in a dose-dependent manner and improved event-free survival in a mouse model of thromboplastin-induced generalized and invariably fatal thromboembolism. To our knowledge, **WHI-P131** is the first anti-thrombotic agent that prevents platelet aggregation by inhibiting JAK3.

ACCESSION NUMBER: 2001:355133 BIOSIS

DOCUMENT NUMBER: PREV200100355133

TITLE: Role of a JAK3-dependent biochemical signaling pathway in platelet activation and aggregation.

AUTHOR(S): Tibbles, Heather E.; Vassilev, Alexei; Wendorf, Heather; Schonhoff, Dawn; Zhu, Dan; Lorenz, David; Waurzyniak, Barbara; Liu, Xing-Ping; Uckun, Fatih M. (1)

CORPORATE SOURCE: (1) Parker Hughes Inst., 2665 Long Lake Rd., Suite 330, St. Paul, MN, 55113: fatih.uckun@ih.org USA

SOURCE: Journal of Biological Chemistry, (May 25, 2001) Vol. 276, No. 21, pp. 17815-17822. print.

ISSN: 0021-9258.

DOCUMENT TYPE: Article

LANGUAGE: English

SUMMARY LANGUAGE: English

L1 ANSWER 28 OF 52 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

TI Prevention of fatal thromboembolism in mice by selectively targeting BTK and TEC kinases in platelets with alpha-cyano-beta-hydroxy-beta-methyl-N-(2,5-dibromophenyl)-propenamide (LFM-A13).

AB The leflunomide metabolite analog alpha-cyano-beta-hydroxy-beta-methyl-N-(2,5-dibromophenyl)-propenamide (LFM-A13) is a rationally designed specific inhibitor of the Bruton's tyrosine kinase (BTK) and TEC kinase. Since BTK and TEC play an important role in platelet physiology by regulating the glycoprotein GPIIb/IIIa-coupled collagen receptor signaling pathway, we sought to determine the effects of LFM-A13 on platelet activation and aggregation in vitro as well as bleeding time and thromboplastin-induced fatal thromboembolism in vivo. At low micromolar concentrations, LFM-A13 inhibited collagen-induced BTK/TEC stimulation and BTK/TEC-dependent downstream signaling events, including tyrosine phosphorylation of phospholipase C gamma 2 (PLCgamma2), activation of phosphoinositide turnover with increased inositol triphosphate (Ins-1,4,5-P3) production and degranulation/serotonin release. Following collagen stimulation, LFM-A13-treated platelets did not undergo shape or biochemical changes indicative of activation, such as membrane ruffling, pseudopod formation, or translocation of cytoplasmic HIC-5 and SYK proteins to the cytoskeleton. LFM-A13 inhibited collagen-induced (but not thrombin-induced) platelet aggregation with an IC50 value of 2.8 muM. In contrast to LFM-A13, the Janus kinase 3 inhibitor **WHI-P131** did not affect collagen-induced platelet aggregation. LFM-A13 was not toxic to mice when administered systemically at dose levels ranging from 1 mg/kg to 100 mg/kg. Highly effective platelet inhibitory plasma concentrations (gtoreq10 muM) of LFM-A13 can be achieved in mice without toxicity. At nontoxic dose levels, LFM-A13 prolonged the tail



bleeding time of mice in dose-dependent manner and markedly improved survival in a mouse model of thromboplastin-induced generalized and fatal thromboembolism. The probability of EFS after the thromboplastin challenge was 10+-7% (median survival time=2.5 min), for the vehicle-treated control group (N=20), 30+-15 (median survival time=5.3 min) for warfarin-treated control group (N=20) (P=0.001), 50+-16% (median survival time = 8.0 min) for LFM-A13 at the 25 mg/kg dose level (N=10) (P=0.09), and 80+-13% (median survival time >48 hours) for LFM-A13 at the 50 mg/kg dose level (N=10) (P=0.01). To our knowledge, LFM-A13 is the first anti-thrombotic agent which prevents platelet aggregation by inhibiting BTK and TEC kinases.

ACCESSION NUMBER: 2001:311609 BIOSIS  
DOCUMENT NUMBER: PREV200100311609  
TITLE: Prevention of fatal thromboembolism in mice by selectively targeting BTK and TEC kinases in platelets with alpha-cyano-beta-hydroxy-beta-methyl-N-(2,5-dibromophenyl)-propenamide (LFM-A13).  
AUTHOR(S): Tibbles, Heather E. (1); Vassilev, Alexei O. (1); Wendorf, Heather (1); Zhu, Dan (1); Bartell, Steve (1); Lorenz, David (1); Waurzyniak, Barbara (1); Zheng, Yagou (1); Mahajan, Sandeep (1); Uckun, Fatih M. (1)  
CORPORATE SOURCE: (1) Parker Hughes Institute, St Paul, MN USA  
SOURCE: Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 275a. print.  
Meeting Info.: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000 American Society of Hematology . ISSN: 0006-4971.  
DOCUMENT TYPE: Conference  
LANGUAGE: English  
SUMMARY LANGUAGE: English

L1 - ANSWER 29 OF 52 - BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.  
TI Prevention of fatal thromboembolism in mice by selectively targeting Jak 3 kinase in platelets with 4-(4'-Hydroxylphenyl)-amino-6,7-dimethoxyquinazoline (WHI-P131).  
AB The quinazoline derivative, 4-(4'-Hydroxylphenyl)-amino-6,7-dimethoxyquinazoline (WHI-P131) is a rationally designed specific inhibitor of Janus Kinase 3. We sought to determine the effects of WHI-P131 on platelet activation and aggregation in vitro as well as bleeding time and thromboplastin-induced fatal thromboembolism in vivo. At low micromolar concentrations, WHI-P131 inhibited thrombin-induced signaling events, including degranulation/serotonin release, membrane ruffling, pseudopod formation, and translocation of cytoplasmic proteins to the Tx-soluble and insoluble cytoskeleton. Thrombin-induced tyrosine phosphorylation as well as membrane localization of Stat 1 and Stat3beta were also markedly inhibited by WHI-P131. WHI-P131 inhibited thrombin-induced (but not collagen-induced) platelet aggregation with an IC50 value of 1.5 muM. Jak 3 deficient mice also exhibited a decrease in thrombin-induced platelet aggregation, overall tyrosine phosphorylation and phosphorylation of Stat 1 and Stat3beta. WHI-P131 was not toxic to mice when administered systemically at dose levels ranging from 1 mg/kg to 250 mg/kg. Highly effective platelet inhibitory plasma concentrations (gtoreq10 muM) of WHI-P131 could be achieved in mice without toxicity. At nontoxic dose levels, WHI-P131 prolonged the tail bleeding time of mice in dose-dependent manner and improved survival in a mouse model of thromboplastin-induced generalized and fatal thromboembolism. The probability of EFS after the thromboplastin challenge was 10+-7% (median survival time=2.5 min) for the vehicle-treated control group (N=20), 30+-15 (median survival time=5.3 min) for warfarin-treated control group (N=20) (P=0.001), and 30+-17% (median survival time =5.2 min) for the WHI-P131-treated test group (25 mg/kg dose level; N=10)

(P=0.001) This present study significantly expands our knowledge of the importance of Jak3 and the Stat family proteins in platelets. To our knowledge, WHI-P131 is the first anti-thrombotic agent which prevents platelet aggregation by inhibiting Jak 3.

ACCESSION NUMBER: 2001:311605 BIOSIS  
DOCUMENT NUMBER: PREV200100311605  
TITLE: Prevention of fatal thromboembolism in mice by selectively targeting Jak 3 kinase in platelets with 4-(4'-Hydroxyphenyl)-amino-6,7-dimethoxyquinazoline (WHI-P131).  
AUTHOR(S): Tibbles, Heather E. (1); Vassilev, Alexei O. (1); Wendorf, Heather (1); Lorenz, David (1); Zhu, Dan (1); Waurzyniak, Barbara (1); Liu, Xing-Ping (1); Uckun, Fatih M. (1)  
CORPORATE SOURCE: (1) Parker Hughes Institute, St. Paul, MN USA  
SOURCE: Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 273a. print.  
Meeting Info.: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000 American Society of Hematology . ISSN: 0006-4971.  
DOCUMENT TYPE: Conference  
LANGUAGE: English  
SUMMARY LANGUAGE: English

L1 ANSWER 30 OF 52 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

TI Prevention of development of type 1 diabetes in NOD mice by targeting Janus kinase (JAK)3 with 4-(4'-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline (WHI-P131).

ACCESSION NUMBER: 2001:2325 BIOSIS  
DOCUMENT NUMBER: PREV200100002325  
TITLE: Prevention of development of type 1 diabetes in NOD mice by targeting Janus kinase (JAK)3 with 4-(4'-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline (WHI-P131).

AUTHOR(S): Cetkovic-Cvrlje, Marina (1); Dragt, Angela L. (1); Uckun, Fatih M.  
CORPORATE SOURCE: (1) Department of Diabetes and Transplantation, Parker Hughes Institute, Saint Paul, MN USA  
SOURCE: Diabetes Research and Clinical Practice, (September, 2000) Vol. 50, No. Suppl. 1, pp. S183. print.  
Meeting Info.: 17th International Diabetes Federation Congress on Diabetes Research and Clinical Practice. Mexico-City, Mexico November 05-10, 2000  
ISSN: 0168-8227.  
DOCUMENT TYPE: Conference  
LANGUAGE: English  
SUMMARY LANGUAGE: English

L1 ANSWER 31 OF 52 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

TI Islet allograft rejection is prevented by targeting Janus kinase 3 with 4-(4'-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline (WHI-P131).

ACCESSION NUMBER: 2001:2323 BIOSIS  
DOCUMENT NUMBER: PREV200100002323  
TITLE: Islet allograft rejection is prevented by targeting Janus kinase 3 with 4-(4'-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline (WHI-P131).  
AUTHOR(S): Cetkovic-Cvrlje, Marina (1); Olson, Christine M. (1); Dragt, Angela L. (1); Uckun, Fatih M.  
CORPORATE SOURCE: (1) Department of Diabetes and Transplantation, Parker Hughes Institute, Saint Paul, MN USA  
SOURCE: Diabetes Research and Clinical Practice, (September, 2000) Vol. 50, No. Suppl. 1, pp. S183. print.  
Meeting Info.: 17th International Diabetes Federation

Congress on Diabetes Research and Clinical Practice  
Mexico-City, Mexico November 05-10, 2000  
ISSN: 0168-8227.

DOCUMENT TYPE: Conference  
LANGUAGE: English  
SUMMARY LANGUAGE: English

L1 ANSWER 32 OF 52 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.  
TI A specific inhibitor of Janus kinase-3 increases survival in a transgenic mouse model of amyotrophic lateral sclerosis.  
AB Amyotrophic lateral sclerosis (ALS) is a progressive, fatal neurodegenerative disorder involving the motor neurons of cortex, brain stem, and spinal cord. About 10% of all ALS patients are familial cases (FALS), of which 20% have mutations in the Cu,Zn-superoxide dismutase (SOD1) gene. The murine model for FALS, which overexpresses a FALS variant of the SOD1 gene, exhibits progressive limbic paralysis followed by death. Treatment of FALS mice with WHI-P131, a specific inhibitor of Janus kinase 3 (JAK3), increased survival by more than two months, suggesting that specific inhibitors of JAK3 may be useful in the treatment of human ALS. These results uniquely establish JAK3 as a novel molecular target for the treatment of FALS.

ACCESSION NUMBER: 2000:221257 BIOSIS  
DOCUMENT NUMBER: PREV200000221257  
TITLE: A specific inhibitor of Janus kinase-3 increases survival in a transgenic mouse model of amyotrophic lateral sclerosis.  
AUTHOR(S): Trieu, Vuong N.; Liu, Rugao; Liu, Xing-Ping; Uckun, Fatih M. (1)  
CORPORATE SOURCE: (1) Hughes Institute, 2665 Long Lake Road, Saint Paul, MN, 55113 USA  
SOURCE: Biochemical and Biophysical Research Communications, (Jan. 7, 2000) Vol. 267, No. 1, pp. 22-25.  
ISSN: 0006-291X.  
DOCUMENT TYPE: Article  
LANGUAGE: English  
SUMMARY LANGUAGE: English

L1 ANSWER 33 OF 52 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.  
TI Pharmacokinetics and in vivo toxicity of Janus kinase 3 (JAK3) inhibitor WHI-P131 (4-(4'-hydroxyphenyl)-amino-6,7-Dimethoxyquinazoline.

ACCESSION NUMBER: 2000:45417 BIOSIS  
DOCUMENT NUMBER: PREV200000045417  
TITLE: Pharmacokinetics and in vivo toxicity of Janus kinase 3 (JAK3) inhibitor WHI-P131 (4-(4'-hydroxyphenyl)-amino-6,7-Dimethoxyquinazoline.  
AUTHOR(S): Uckun, F. M. (1); Ek, O.; Liu, X.-P.; Chen, C.-L.  
CORPORATE SOURCE: (1) Dept. of Oncology, Drug Discovery Program, Parker Hughes Cancer Center, Hughes Institute, Saint Paul, MN USA  
SOURCE: Blood, (Nov. 15 ) Vol. 94, No. 10 SUPPL. 1 PART 2, pp. 197b.  
Meeting Info.: Forty-first Annual Meeting of the American Society of Hematology New Orleans, Louisiana, USA December 3-7, 1999 The American Society of Hematology  
. ISSN: 0006-4971.

DOCUMENT TYPE: Conference  
LANGUAGE: English

L1 ANSWER 34 OF 52 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.  
TI Anti-leukemic agents targeting Janus kinase 3 (JAK3).  
ACCESSION NUMBER: 2000:45416 BIOSIS  
DOCUMENT NUMBER: PREV200000045416  
TITLE: Anti-leukemic agents targeting Janus kinase 3 (JAK3).  
AUTHOR(S): Sudbeck, E. A. (1); Liu, X.-P.; Narla, R. K.; Mahajan, S.;

CORPORATE SOURCE: Ghosh, S.; Mao, C.; Uckun, F. M.  
(1) Department of Structural Biology, Drug Discovery  
Program, Parker Hughes Cancer Center, Hughes Institute,  
Saint Paul, MN USA  
SOURCE: Blood, (Nov. 15 ) Vol. 94, No. 10 SUPPL. 1 PART  
2, pp. 196b.  
Meeting Info.: Forty-first Annual Meeting of the American  
Society of Hematology New Orleans, Louisiana, USA December  
3-7, 1999 The American Society of Hematology  
. ISSN: 0006-4971.  
DOCUMENT TYPE: Conference  
LANGUAGE: English

L1 ANSWER 35 OF 52 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

TI Structural characterization of anti-leukemic agent WHI-  
P131, an inhibitor of Janus kinase 3 (JAK3).

ACCESSION NUMBER: 2000:45415 BIOSIS

DOCUMENT NUMBER: PREV200000045415

TITLE: Structural characterization of anti-leukemic agent  
WHI-P131, an inhibitor of Janus kinase 3  
(JAK3).

AUTHOR(S): Sudbeck, E. A. (1); Jennissen, J. D.; Liu, X.-P.; Uckun, F.  
M.

CORPORATE SOURCE: (1) Department of Structural Biology, Drug Discovery  
Program, Parker Hughes Cancer Center, Hughes Institute,  
Saint Paul, MN USA

SOURCE: Blood, (Nov. 15 ) Vol. 94, No. 10 SUPPL. 1 PART  
2, pp. 196b.  
Meeting Info.: Forty-first Annual Meeting of the American  
Society of Hematology New Orleans, Louisiana, USA December  
3-7, 1999 The American Society of Hematology  
. ISSN: 0006-4971.

DOCUMENT TYPE: Conference

LANGUAGE: English

L1 ANSWER 36 OF 52 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

TI Targeting Janus kinase 3 in mast cells prevents immediate hypersensitivity  
reactions and anaphylaxis.

AB Janus kinase 3 (JAK3), a member of the Janus family protein-tyrosine  
kinases, is expressed in mast cells, and its enzymatic activity is  
enhanced by IgE receptor/FcepsilonRI cross-linking. Selective inhibition  
of JAK3 in mast cells with 4-(4'-hydroxyphenyl)-amino-6,7-  
dimethoxyquinazoline (WHI-P131) blocked the  
phospholipase C activation, calcium mobilization, and activation of  
microtubule-associated protein kinase after IgE receptor/FcepsilonRI  
cross-linking. Treatment of IgE-sensitized rodent as well as human mast  
cells with WHI-P131 effectively inhibited the  
activation-associated morphological changes, degranulation, and  
proinflammatory mediator release after specific antigen challenge without  
affecting the functional integrity of the distal secretory machinery. In  
vivo administration of the JAK3 inhibitor WHI-P131  
prevented mast cell degranulation and development of cutaneous as well as  
systemic fatal anaphylaxis in mice at nontoxic dose levels. Thus, JAK3  
plays a pivotal role in IgE receptor/FcepsilonRI-mediated mast cell  
responses, and targeting JAK3 with a specific inhibitor, such as  
WHI-P131, may provide the basis for new and effective  
treatment as well as prevention programs for mast cell-mediated allergic  
reactions.

ACCESSION NUMBER: 1999:482894 BIOSIS

DOCUMENT NUMBER: PREV199900482894

TITLE: Targeting Janus kinase 3 in mast cells prevents immediate  
hypersensitivity reactions and anaphylaxis.

AUTHOR(S): Malaviya, Ravi; Zhu, DeMin; Dibirdik, Ilker; Uckun, Fatih  
M. (1)

CORPORATE SOURCE: (1) Hughes Inst., 2665 Long Lake Rd., Suite 330, Saint Paul, MN, 55113 USA  
SOURCE: Journal of Biological Chemistry, (Sept. 17, 1999) Vol. 274, No. 38, pp. 27028-27038.  
ISSN: 0021-9258.  
DOCUMENT TYPE: Article  
LANGUAGE: English  
SUMMARY LANGUAGE: English

L1 ANSWER 37 OF 52 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

TI Quantitative high-performance liquid chromatographic method for pharmacokinetic studies of the potent mast cell inhibitor 4-(4'-hydroxyphenyl)amino-6,7-dimethoxyquinazoline (WHI-P131).

AB The novel quinazoline derivative 4-(4'-hydroxyphenyl)amino-6,7-dimethoxyquinazoline (WHI-P131) has recently been identified as a potent mast cell inhibitor capable of preventing IgE/antigen induced cutaneous as well as systemic fatal anaphylaxis in mice. Here we describe a sensitive high-performance liquid chromatography (HPLC)-based quantitative detection method for measurement of WHI-P131 levels in plasma as well as in target mast cells. The average extraction recovery for WHI-P131 was 88.4% for plasma and 75.7% for RBL-2H3 mast cell lysates. Good linearity ( $r > 0.999$ ) was observed throughout the concentration range of 0.1-20  $\mu\text{M}$  in plasma and 0.01-5 nmol in 5cndot106 cells (0.5-238  $\mu\text{M}$  per cell) for WHI-P131. Intra- and inter-assay variabilities were  $< 7\%$  and the lowest detection limit of WHI-P131 was 0.05  $\mu\text{M}$  in plasma and 0.005 nmol in 5 million cells, respectively, at a signal-to-noise ratio of approx 2. The practical utility of this new HPLC method was confirmed in a pilot pharmacokinetic study in BALB/c mice as well as in a cellular drug uptake and disposition study in RBL-2H3 mast cells. After intraperitoneal administration of a non-toxic 40 mg/kg bolus dose of WHI-P131, the estimated maximum plasma concentration was 92.7  $\mu\text{M}$ , which is approximately 1-log higher than the effective in vitro mast cell inhibitory concentrations of WHI-P131. The drug absorption was rapid with an absorption half-life of only 2.9 min and the estimated time to reach the maximum plasma concentration was 8.3 min. WHI-P131 was cleared with an apparent systemic clearance rate of 2586 ml/h/kg and an elimination half-life of 1.8 h. An intracellular exposure level (AUC) of 55  $\mu\text{M}$  cndoth was obtained after in vitro treatment of RBL-2H3 mast cells with WHI-P131 at a 33.6  $\mu\text{M}$  final concentration in culture medium. The availability of the described quantitative HPLC detection method for WHI-P131 provides the basis for further development of WHI-P131 as an anti-allergic drug through detailed pharmacodynamic studies in preclinical animal models.

ACCESSION NUMBER: 1999:256617 BIOSIS  
DOCUMENT NUMBER: PREV199900256617  
TITLE: Quantitative high-performance liquid chromatographic method for pharmacokinetic studies of the potent mast cell inhibitor 4-(4'-hydroxyphenyl)amino-6,7-dimethoxyquinazoline (WHI-P131).  
AUTHOR(S): Chen, Chun-Lin; Malaviya, Ravi; Chen, Hao; Liu, Xing-Ping; Uckun, Fatih M. (1)  
CORPORATE SOURCE: (1) Department of Pharmaceutical Sciences, Hughes Institute, Saint Paul, MN USA  
SOURCE: Journal of Chromatography B, (April 30, 1999) Vol. 727, No. 1-2, pp. 205-212.  
ISSN: 0378-4347.  
DOCUMENT TYPE: Article  
LANGUAGE: English  
SUMMARY LANGUAGE: English

L1 ANSWER 38 OF 52 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

TI Structural basis for potent and selective inhibition of Janus kinase 3 (JAK3) by anti-leukemic agent WHI-P131.  
ACCESSION NUMBER: 1999:167892 BIOSIS  
DOCUMENT NUMBER: PREV199900167892  
TITLE: Structural basis for potent and selective inhibition of Janus kinase 3 (JAK3) by anti-leukemic agent WHI-P131.  
AUTHOR(S): Sudbeck, Elise A.; Liu, Xing-Ping; Mahajan, Sandee; Mao, Chen; Uckun, Fatih M.  
CORPORATE SOURCE: Hughes Inst., St. Paul, MN 55113 USA  
SOURCE: Abstracts of Papers American Chemical Society, (1999) Vol. 217, No. 1-2, pp. MEDI 59.  
Meeting Info.: 217th National Meeting of the American Chemical Society Anaheim, California, USA March 21-25, 1999 American Chemical Society  
. ISSN: 0065-7727.  
DOCUMENT TYPE: Conference  
LANGUAGE: English

L1 ANSWER 39 OF 52 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.  
TI Structure based design of specific inhibitors of Janus kinase 3 (Jak3) as potent anti-leukemic agents.  
ACCESSION NUMBER: 1999:106005 BIOSIS  
DOCUMENT NUMBER: PREV199900106005  
TITLE: Structure based design of specific inhibitors of Janus kinase 3 (Jak3) as potent anti-leukemic agents.  
AUTHOR(S): Sudbeck, E. (1); Mao, C.; Liu, X. P.; Narla, R. K.; Chen, C. L.; Waurzyniak, B.; Uckun, F. M.  
CORPORATE SOURCE: (1) Parker Hughes Cancer Cent., Drug Discovery Program, Dep. Structural Biol., Hughes Inst., St. Paul, MN USA  
SOURCE: Blood, (Nov. 15, 1998) Vol. 92, No. 10 SUPPL. 1 PART 1-2, pp. 599A.  
Meeting Info.: 40th Annual Meeting of the American Society of Hematology Miami Beach, Florida, USA December 4-8, 1998 The American Society of Hematology  
. ISSN: 0006-4971.  
DOCUMENT TYPE: Conference  
LANGUAGE: English

L1 ANSWER 40 OF 52 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.  
TI Targeting the Raf kinase cascade in cancer therapy - Novel molecular targets and therapeutic strategies.  
AB The mitogen-activated protein kinases (MAPKs) are a group of signal transducers with oncogenic potential in an assortment of cell types. Dysregulated signalling from any of the members of this family has been shown to result in development of human malignancies. Consequently, the collective goal of the scientific community is to inhibit aberrant signalling initiated from these molecules whilst minimising toxicity associated with such inhibition. This review covers events responsible for MAPK activation in detail, with an emphasis placed upon possible points of pharmacological intervention. A discussion addressing numerous chemotherapeutic approaches that have been developed over the previous decade for MAPK inhibition is also included. In addition, emphasis is placed upon the various arrays of kinase inhibitors, small molecule inhibitors, competitive inhibitors, nucleic acid aptamers and other molecules which have been proven effective in prevention of MAPK signalling. Finally, the potential therapeutic promise of many of these compounds is addressed in a manner that encompasses the complexities of MAPK signal transduction, in addition to concerns surrounding the development of drug resistance.  
ACCESSION NUMBER: 2003019434 EMBASE  
TITLE: Targeting the Raf kinase cascade in cancer therapy - Novel molecular targets and therapeutic strategies.  
AUTHOR: Lee Jr. J.T.; McCubrey J.A.

CORPORATE SOURCE: Dr. J.A. McCubrey, Dept. of Microbiology and Immunology,  
Brody School of Medicine, East Carolina University,  
Greenville, NC, United States. mccubreyj@mail.ecu.edu

SOURCE: Expert Opinion on Therapeutic Targets, (2002) 6/6  
(659-678).  
Refs: 113  
ISSN: 1472-8222 CODEN: EOTTAO

COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 016 Cancer  
030 Pharmacology  
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

L1 ANSWER 41 OF 52 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.

TI Janus kinase 3 inhibitor WHI-P131/JANEX-1 prevents  
graft-versus-host disease but spares the graft-versus-leukemia function of  
the bone marrow allografts in a murine bone marrow transplantation model.

AB The purpose of the present study was to evaluate the effects of  
graft-versus-host disease (GVHD) prophylaxis with the Janus kinase 3  
(JAK3) inhibitor WHI-P131/JANEX-1 on the  
graft-versus-leukemic (GVL) function of marrow allografts in mice  
undergoing bone marrow transplantation (BMT) after being challenged with  
an otherwise invariably fatal dose of BCL-1 leukemia cells. GVHD  
prophylaxis using WHI-P131 markedly improved the  
survival outcome after BMT. The probability of survival at 30 days after  
BMT was 11% +/- 6% for vehicle-treated recipients (median survival time,  
25 days) versus 63% +/- 12% for recipients treated with WHI-  
P131 (median survival time, 36 days; P < .0001). Because  
WHI-P131 is devoid of antileukemic activity against  
BCL-1 leukemia cells, this marked improvement in survival outcome was due  
to reduced incidence of GVHD-associated fatalities combined with sustained  
GVL function of the allografts in the WHI-P131 group.  
Notably, adoptive transfer experiments demonstrated that the spleens of  
WHI-P131-treated allograft recipients contained less  
than 0.001% BCL-1 cells. Notably, GVHD prophylaxis with WHI-  
P131 plus methotrexate resulted in 100% survival of mice receiving  
allotransplants challenged with an otherwise invariably fatal dose of  
BCL-1 leukemia. Taken together, our results provide strong experimental  
evidence that GVHD prophylaxis using WHI-P131 does not  
impair the GVL function of the allografts and consequently contributes to  
an improved post-BMT survival outcome of the recipient mice. .COPYRGT.  
2002 by The American Society of Hematology.

ACCESSION NUMBER: 2002413511 EMBASE

TITLE: Janus kinase 3 inhibitor WHI-P131  
/JANEX-1 prevents graft-versus-host disease but spares the  
graft-versus-leukemia function of the bone marrow  
allografts in a murine bone marrow transplantation model.

AUTHOR: Uckun F.M.; Roers B.A.; Waurzyniak B.; Liu X.-P.;  
Cetkovic-Cvrlje M.

CORPORATE SOURCE: F.M. Uckun, Parker Hughes Cancer Center, 2665 Long Lake Rd,  
St Paul, MN 55113, United States. fatih\_uckun@ih.org

SOURCE: Blood, (1 Jun 2002) 99/11 (4192-4199).  
Refs: 25  
ISSN: 0006-4971 CODEN: BLOOAW

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 025 Hematology  
026 Immunology, Serology and Transplantation  
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

L1 ANSWER 42 OF 52 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.  
 TI Targeting Janus kinase 3 to attenuate the severity of acute graft-versus-host disease across the major histocompatibility barrier in mice.  
 AB To prevent the development of acute graft-versus-host disease (GVHD) in lethally irradiated C57BL/6 (H-2(b)) recipient mice transplanted with bone marrow-splenocyte grafts from major histocompatibility complex (MHC) disparate BALB/c mice (H-2(d)), recipient mice were treated with the rationally designed JAK3 inhibitor WHI-P131 [4-(4'-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline] (20 mg/kg, 3 times a day [tid]) daily from the day of bone marrow transplantation (BMT) until the end of the 85-day observation period. Total body irradiation (TBI)-conditioned, vehicle-treated control C57BL/6 mice (n = 38) receiving bone marrow-splenocyte grafts from BALB/c mice survived acute TBI toxicity, but they all developed histologically confirmed severe multiorgan GVHD and died after a median survival time of 37 days. WHI-P131 treatment (20 mg/kg intraperitoneally, tid) prolonged the median survival time of the BMT recipients to 56 days. The probability of survival at 2 months after BMT was 11% +/- 5% for vehicle-treated control mice (n = 38) and 41% +/- 9% for mice treated with WHI-P131 (n = 32) (P < .0001). Notably, the combination regimen WHI-P131 plus the standard anti-GVHD drug methotrexate (MTX) (10 mg/m(2) per day) was more effective than WHI-P131 or MTX alone. More than half the C57BL/6 recipients receiving this most effective GVHD prophylaxis remained alive and healthy throughout the 85-day observation period, with a cumulative survival probability of 70% +/- 10%. Taken together, these results indicate that targeting JAK3 in alloreactive donor lymphocytes with a chemical inhibitor such as WHI-P131 may attenuate the severity of GVHD after BMT. .COPYRGT. 2001 by The American Society of Hematology.

ACCESSION NUMBER: 2002355011 EMBASE  
 TITLE: Targeting Janus kinase 3 to attenuate the severity of acute graft-versus-host disease across the major histocompatibility barrier in mice.  
 AUTHOR: Cetkovic-Cvrlje M.; Roers B.A.; Waurzyniak B.; Liu X.-P.; Uckun F.M.  
 CORPORATE SOURCE: F.M. Uckun, Parker Hughes Institute, 2665 Long Lake Rd, St Paul, MN 55113, United States. fatih\_uckun@ih.org  
 SOURCE: Blood, (1 Sep 2001) 98/5 (1607-1613).  
 Refs: 37  
 ISSN: 0006-4971 CODEN: BLOOAW  
 COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article  
 FILE SEGMENT: 005 General Pathology and Pathological Anatomy  
 025 Hematology  
 026 Immunology, Serology and Transplantation  
 037 Drug Literature Index  
 LANGUAGE: English  
 SUMMARY LANGUAGE: English

L1 ANSWER 43 OF 52 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.  
 TI The Raf/MEK/ERK signal transduction cascade as a target for chemotherapeutic intervention in leukemia.  
 AB The Raf/MEK/ERK (MAPK) signal transduction cascade is a vital mediator of a number of cellular fates including growth, proliferation and survival, among others. The focus of this review centers on the MAPK signal transduction pathway, its mechanisms of activation, downstream mediators of signaling, and the transcription factors that ultimately alter gene expression. Furthermore, negative regulators of this cascade, including phosphatases, are discussed with an emphasis placed upon chemotherapeutic intervention at various points along the pathway. In addition, mounting evidence suggests that the PI3K/Akt pathway may play a role in the effects elicited via MAPK signaling; as such, potential interactions and their possible cellular ramifications are discussed.



ACCESSION NUMBER: 2002155331 EMBASE  
 TITLE: The Raf/MEK/ERK signal transduction cascade as a target for chemotherapeutic intervention in leukemia.  
 AUTHOR: Lee Jr. J.T.; McCubrey J.A.  
 CORPORATE SOURCE: J.A. McCubrey, Dept. of Microbiology/Immunology, Brody School of Medicine, East Carolina University, Greenville, NC 27858, United States  
 SOURCE: Leukemia, (2002) 16/4 (486-507).  
 Refs: 379  
 ISSN: 0887-6924 CODEN: LEUKED  
 COUNTRY: United Kingdom  
 DOCUMENT TYPE: Journal; General Review  
 FILE SEGMENT: 016 Cancer  
 022 Human Genetics  
 025 Hematology  
 037 Drug Literature Index  
 LANGUAGE: English  
 SUMMARY LANGUAGE: English

L1 ANSWER 44 OF 52 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.  
 TI CYP1A-mediated metabolism of the Janus kinase-3 inhibitor 4-(4'-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline: Structural basis for inactivation by regioselective O-demethylation.  
 AB Here we report the phase I metabolism of the rationally designed Janus kinase-3 (JAK) inhibitor 4-(4'-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline (WHI-P131; JANEX-1). JANEX-1 was metabolized by the cytochrome P450 enzymes CYP1A1 and CYP1A2 in a regioselective fashion to form the biologically inactive 7-O-demethylation product 4-(4'-hydroxyphenyl)-amino-6-methoxy-7-hydroxyquinazoline (JANEX-1-M). Our molecular modeling studies indicated that the CYP1A family enzymes bind and demethylate JANEX-1 at the C-7 position of the quinazoline ring since the alternative binding conformation with demethylation at the C-6 position would result in a severe steric clash with the binding site residues. The metabolism of JANEX-1 to JANEX-1-M in pooled human liver microsomes followed Michaelis-Menten kinetics with V(max) and K(m) values (mean  $\pm$  S.D.) of 34.6  $\pm$  9.8 pmol/min/mg and 107.3  $\pm$  66.3  $\mu$ M, respectively.  $\alpha$ -Naphthoflavone and furafylline, which both inhibit CYP1A2, significantly inhibited the formation of JANEX-1-M in human liver microsomes. There was a direct correlation between CYP1A activities and the magnitude of JANEX-1-M formation in the liver microsomes from different animal species. A significantly increased metabolic rate for JANEX-1 was observed in Aroclor 1254-,  $\beta$ -naphthoflavone-, and 3-methylcholanthrene-induced microsomes but not in clofibrate-, dexamethasone-, isoniazid-, and phenobarbital-induced microsomes. The formation of JANEX-1-M in the presence of baculovirus-expressed CYP1A1 and 1A2 was consistent with Michaelis-Menten kinetics. The systemic clearance of JANEX-1-M was much faster than that of JANEX-1 (5525.1  $\pm$  1926.2 ml/h/kg versus 1458.0  $\pm$  258.6 ml/h/kg). Consequently, the area under the curve value for JANEX-1-M was much smaller than that for JANEX-1 (27.5  $\pm$  8.0 versus 94.8  $\pm$  18.4  $\mu$ M  $\cdot$  h; P  $\leq$  0.001).

ACCESSION NUMBER: 2002006486 EMBASE  
 TITLE: CYP1A-mediated metabolism of the Janus kinase-3 inhibitor 4-(4'-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline: Structural basis for inactivation by regioselective O-demethylation.  
 AUTHOR: Uckun F.M.; Thoen J.; Chen H.; Sudbeck E.; Mao C.; Malaviya R.; Liu X.-P.; Chen C.-L.  
 CORPORATE SOURCE: F.M. Uckun, Parker Hughes Cancer Center, 2665 Long Lake Road, St. Paul, MN 55113, United States. fatih\_uckun@ih.org  
 SOURCE: Drug Metabolism and Disposition, (2002) 30/1 (74-85).  
 Refs: 39  
 ISSN: 0090-9556 CODEN: DMDSAI  
 COUNTRY: United States

DOCUMENT TYPE: Journal; Article  
FILE SEGMENT: 029 Clinical Biochemistry  
030 Pharmacology  
037 Drug Literature Index  
LANGUAGE: English  
SUMMARY LANGUAGE: English

L1 ANSWER 45 OF 52 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.  
TI Structure-based design of potent inhibitors of EGF-receptor tyrosine kinase as anti-cancer agents.  
AB In a systematic effort to design inhibitors of the epidermal growth factor receptor (EGFR) family protein tyrosine kinases (PTK) as anti-cancer agents, we have constructed a three-dimensional homology model of the EGFR kinase domain and used molecular modeling methods for the structure-based design of analogs of the active metabolite of leflunomide (LFM) with potent and specific inhibitory activity against EGFR. These docking studies identified .alpha.-cyano-.beta.-hydroxy-.beta.-methyl-N-[4-(trifluoromethoxy)phenyl]-propenamide (LFM-A12) as our lead compound, which was predicted to bind to the EGFR catalytic site in a planar conformation. LFM-A12 inhibited the proliferation ( $IC_{50} = 26.3 \mu M$ ) and in vitro invasiveness ( $IC_{50} = 28.4 \mu M$ ) of EGFR positive human breast cancer cells in a concentration-dependent fashion. Similarly, the model of the EGFR binding pocket was used in combination with docking procedures to predict the favorable placement of chemical groups with defined sizes at multiple modification sites on another class of EGFR inhibitors, the 4-anilinoquinazoline. This approach has led to the successful design of a dibromo quinazoline derivative, WHI-P97, which had an estimated  $K(i)$  value of  $0.09 \mu M$  from modeling studies and a measured  $IC_{50}$  value of  $2.5 \mu M$  in EGFR kinase inhibition assays. WHI-P97 effectively inhibited the in vitro invasiveness of EGFR-positive human cancer cells in a concentration-dependent manner. However, unlike LFM-A12, the quinazoline compounds are not specific for EGFR.

ACCESSION NUMBER: 2000113082 EMBASE  
TITLE: Structure-based design of potent inhibitors of EGF-receptor tyrosine kinase as anti-cancer agents.  
AUTHOR: Ghosh S.; Narla R.K.; Zheng Y.; Liu X.-P.; Jun X.; Mao C.; Sudbeck E.A.; Uckun F.M.  
CORPORATE SOURCE: F.M. Uckun, Parker Hughes Institute, 2665 Long Lake Road, St Paul, MN 55113, United States  
SOURCE: Anti-Cancer Drug Design, (1999) 14/5 (403-410).  
Refs: 32  
ISSN: 0266-9536 CODEN: ACDDEA  
COUNTRY: United Kingdom  
DOCUMENT TYPE: Journal; Article  
FILE SEGMENT: 016 Cancer  
030 Pharmacology  
037 Drug Literature Index  
LANGUAGE: English  
SUMMARY LANGUAGE: English

L1 ANSWER 46 OF 52 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.  
TI A specific inhibitor of Janus kinase-3 increases survival in a transgenic mouse model of amyotrophic lateral sclerosis.  
AB Amyotrophic lateral sclerosis (ALS) is a progressive, fatal neurodegenerative disorder involving the motor neurons of cortex, brain stem, and spinal cord. About 10 of all ALS patients are familial cases (FALS), of which 20 have mutations in the Cu,Zn-superoxide dismutase (SOD1) gene. The murine model for FALS, which overexpresses a FALS variant of the SOD1 gene, exhibits progressive limbic paralysis followed by death. Treatment of FALS mice with WHI-P131, a specific inhibitor of Janus kinase 3 (JAK3), increased survival by more than two months, suggesting that specific inhibitors of JAK3 may be useful in the treatment of human ALS. These results uniquely establish JAK3 as a novel molecular target for the treatment of FALS. (C) 2000 Academic Press.

ACCESSION NUMBER: 2000049309 EMBASE  
 TITLE: A specific inhibitor of Janus kinase-3 increases survival in a transgenic mouse model of amyotrophic lateral sclerosis.  
 AUTHOR: Trieu V.N.; Liu R.; Liu X.-P.; Uckun F.M.  
 CORPORATE SOURCE: F.M. Uckun, Hughes Institute, 2665 Long Lake Road, St. Paul, MN 55113, United States. fatih-uckun@ih.org  
 SOURCE: Biochemical and Biophysical Research Communications, (7 Jan 2000) 267/1 (22-25).  
 Refs: 34  
 ISSN: 0006-291X CODEN: BBRCA  
 COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article  
 FILE SEGMENT: 008 Neurology and Neurosurgery  
 029 Clinical Biochemistry  
 LANGUAGE: English  
 SUMMARY LANGUAGE: English

L1 ANSWER 47 OF 52 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.  
 TI In vivo toxicity and pharmacokinetic features of the janus kinase 3 inhibitor WHI-P131 [4-(4'Hydroxyphenyl)-amino-6,7-dimethoxyquinazoline].  
 AB 4-(4'Hydroxyphenyl)-amino-6,7-dimethoxyquinazoline (WHI-P131) is a potent and selective inhibitor of the Janus kinase 3, which triggers apoptosis in human acute lymphoblastic leukemia (ALL) cells. In this preclinical study, we evaluated the pharmacokinetics and toxicity of WHI-P131 in rats, mice, and cynomolgus monkeys. Following i.v. administration, the terminal elimination half-life of WHI-P131 was 73.2 min in rats, 103.4 min in mice, and 45.0 min in monkeys. The i.v. administered WHI-P131 showed a very wide tissue distribution in mice. Following i.p. administration, WHI-P131 was rapidly absorbed in both rats and mice, and the time to reach the maximum plasma concentration (t(max)) was 24.8 min in rats and 10.0 min in mice. Subsequently, WHI-P131 was eliminated with a terminal elimination half-life of 51.8 min in rats and 123.6 min in mice. The estimated i.p. bioavailability was 95% for rats, as well as for mice. WHI-P131 was quickly absorbed after oral administration in mice with a t(max) of 5.8 min, but its oral bioavailability was relatively low (29.6%). The elimination half-life of WHI-P131 after oral administration was 297.6 min. WHI-P131 was not acutely toxic to mice at single i.p. bolus doses ranging from 0.5-250 mg/kg. Two cynomolgus monkeys treated with 20 mg/kg WHI-P131 and one cynomolgus monkey treated with 100 mg/kg WHI-P131 experienced no side effects. Plasma samples from WHI-P131-treated monkeys exhibited potent antileukemic activity against human ALL cells in vitro. To our knowledge, this is the first preclinical toxicity and pharmacokinetic study of a Janus kinase 3 inhibitor. Further development of WHI-P131 may provide the basis for new and effective treatment programs for relapsed ALL in clinical settings.

ACCESSION NUMBER: 1999367341 EMBASE  
 TITLE: In vivo toxicity and pharmacokinetic features of the janus kinase 3 inhibitor WHI-P131 [4-(4'Hydroxyphenyl)-amino-6,7-dimethoxyquinazoline].  
 AUTHOR: Uckun F.M.; Ek O.; Liu X.-P.; Chen C.-L.  
 CORPORATE SOURCE: F.M. Uckun, Hughes Institute, 2665 Long Lake Road, St. Paul, MN 55113, United States  
 SOURCE: Clinical Cancer Research, (1999) 5/10 (2954-2962).  
 Refs: 20  
 ISSN: 1078-0432 CODEN: CCREF4  
 COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article  
 FILE SEGMENT: 016 Cancer

030 Pharmacology  
037 Drug Literature Index

LANGUAGE: English  
SUMMARY LANGUAGE: English

L1 ANSWER 48 OF 52 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.

TI Recent advances in JAK3 kinase inhibitors.

AB The Janus family of tyrosine kinases (JAKs) has emerged as a promising target for therapeutic agents. JAKs are involved in pathways which help regulate cellular functions in the lympho-hematopoietic system critical for cell proliferation and cell survival. JAKs are abundantly expressed in primary leukemic cells from children with acute lymphoblastic leukemia (ALL) and are involved in signals regulating apoptosis. Two recently reported dimethoxyquinazoline compounds, **WHI-P131** and **WHI-P154** (Hughes Institute), were found to inhibit JAK3 but not JAK1 or JAK2. The high potency and selectivity of **WHI-P131** for JAK3 makes it a promising candidate for new treatment strategies against ALL, the most common form of childhood cancer. In addition to its antileukemic properties, **WHI-P131** also shows clinical potential for the treatment of mast cell-mediated immediate hypersensitivity reactions and allergic disorders, including asthma, as well as immunosuppression of alloimmune and autoimmune disorders.

ACCESSION NUMBER: 1999336890 EMBASE

TITLE: Recent advances in JAK3 kinase inhibitors.

AUTHOR: Sudbeck E.A.; Uckun F.M.

CORPORATE SOURCE: F.M. Uckun, Parker Hughes Cancer Center, Hughes Institute, 2665 Long Lake Road, St Paul, MN 55113, United States

SOURCE: IDrugs, (1999) 2/10 (1026-1030).

Refs: 59

ISSN: 1369-7056 CODEN: IDRUFN

COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 016 Cancer  
025 Hematology  
026 Immunology, Serology and Transplantation  
030 Pharmacology  
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

L1 ANSWER 49 OF 52 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.

TI Targeting Janus kinase 3 in mast cells prevents immediate hypersensitivity reactions and anaphylaxis.

AB Janus kinase 3 (JAK3), a member of the Janus family protein-tyrosine kinases, is expressed in mast cells, and its enzymatic activity is enhanced by IgE receptor/Fc.epsilon.RI cross-linking. Selective inhibition of JAK3 in mast cells with 4-(4'-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline (**WHI-P131**) blocked the phospholipase C activation, calcium mobilization, and activation of microtubule-associated protein kinase after IgE receptor/Fc.epsilon.RI cross-linking. Treatment of IgE-sensitized rodent as well as human mast cells with **WHI-P131** effectively inhibited the activation-associated morphological changes, degranulation, and proinflammatory mediator release after specific antigen challenge without affecting the functional integrity of the distal secretory machinery. In vivo administration of the JAK3 inhibitor **WHI-P131** prevented mast cell degranulation and development of cutaneous as well as systemic fatal anaphylaxis in mice at nontoxic dose levels. Thus, JAK3 plays a pivotal role in IgE receptor/Fc.epsilon.RI-mediated mast cell responses, and targeting JAK3 with a specific inhibitor, such as **WHI-P131**, may provide the basis for new and effective treatment as well as prevention programs for mast cell-mediated allergic reactions.

ACCESSION NUMBER: 1999326726 EMBASE

TITLE: Targeting Janus kinase 3 in mast cells prevents immediate hypersensitivity reactions and anaphylaxis.  
 AUTHOR: Malaviya R.; Zhu D.; Dibirdik I.; Uckun F.M.  
 CORPORATE SOURCE: F.M. Uckun, Hughes Inst., 2665 Long Lake Rd., St. Paul, MN 55113, United States  
 SOURCE: Journal of Biological Chemistry, (17 Sep 1999) 274/38 (27028-27033).  
 Refs: 53  
 ISSN: 0021-9258 CODEN: JBCHA3  
 COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article  
 FILE SEGMENT: 026 Immunology, Serology and Transplantation  
 029 Clinical Biochemistry  
 037 Drug Literature Index  
 LANGUAGE: English  
 SUMMARY LANGUAGE: English

L1 ANSWER 50 OF 52 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.  
 TI Structure-based design of specific inhibitors of Janus kinase 3 as apoptosis-inducing antileukemic agents.  
 AB A novel homology model of the kinase domain of Janus kinase (JAK) 3 was used for the structure-based design of dimethoxyquinazoline compounds with potent and specific inhibitory activity against JAK3. The active site of JAK3 in this homology model measures roughly 8 .ANG. x 11 .ANG. x 20 .ANG., with a volume of .apprx.530 .ANG.<sup>3</sup> available for inhibitor binding. Modeling studies indicated that 4-(phenyl)-amino-6,7-dimethoxyquinazoline (parent compound WHI-258) would likely fit into the catalytic site of JAK3 and that derivatives of this compound that contain an OH group at the 4' position of the phenyl ring would more strongly bind to JAK3 because of added interactions with Asp-967, a key residue in the catalytic site of JAK3. These predictions were consistent with docking studies indicating that compounds containing a 4'-OH group, **WHI-P131** [4-(4'-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline], WHI-P154 [4-(3'-bromo-4'-hydroxylphenyl)-amino-6,7-dimethoxyquinazoline], and WHIP97 [4-(3',5'-dibromo-4'-hydroxylphenyl)-amino-6,7-dimethoxyquinazoline], were likely to bind favorably to JAK3, with estimated K(f)s ranging from 0.6 to 2.3 .mu.M. These compounds inhibited JAK3 in immune complex kinase assays in a dose-dependent fashion. In contrast, compounds lacking the 4'-OH group, WHI-P79 [4-(3'-bromophenyl)-amino-6,7-dimethoxyquinazoline], WHI-P111 [4-(3'-bromo-4'-methylphenyl)-amino-6,7-dimethoxyquinazoline], WHI-P112 [4-(2',5'-dibromophenyl)-amino-6,7-dimethoxyquinazoline], WHI-P132 [4-(2'-hydroxylphenyl)-amino-6,7-dimethoxyquinazoline], and WHI-P258 [4-(phenyl)-amino-6,7-dimethoxyquinazoline], were predicted to bind less strongly, with estimated K(i)s ranging from 28 to 72 .mu.M. These compounds did not show any significant JAK3 inhibition in kinase assays. Furthermore, the lead dimethoxyquinazoline compound, **WHI-P131**, which showed potent JAK3-inhibitory activity (IC50 of 78 .mu.M), did not inhibit JAK1 and JAK2, the ZAP/SYK family tyrosine kinase SYK, the TEC family tyrosine kinase BTK, the SRC family tyrosine kinase LYN, or the receptor family tyrosine kinase insulin receptor kinase, even at concentrations as high as 350 .mu.M. **WHI-P131** induced apoptosis in JAK3-expressing human leukemia cell lines NALM-6 and LC1;19 but not in melanoma (M24-MET) or squamous carcinoma (SQ20B) cells. Leukemia cells were not killed by dimethoxyquinazoline compounds that were inactive against JAK3. **WHI-P131** inhibited the donogenic growth of JAK3-positive leukemia cell lines DAUDI, RAMOS, LC1;19, NALM-6, MOLT-3, and HL-60 (but not JAK3-negative BT-20 breast cancer, M24-MET melanoma, or SQ20B squamous carcinoma cell lines) in a concentration-dependent fashion. Potent and specific inhibitors of JAK3 such as WHIP131 may provide the basis for the design of new treatment strategies against acute lymphoblastic leukemia, the most common form of childhood cancer.

ACCESSION NUMBER: 1999213784 EMBASE  
 TITLE: Structure-based design of specific inhibitors of Janus

kinase 3 as apoptosis-inducing antileukemic agents.  
 AUTHOR: Sudbeck E.A.; Liu X.-P.; Narla R.K.; Mahajan S.; Ghosh S.;  
 Mao C.; Uckun F.M.  
 CORPORATE SOURCE: F.M. Uckun, Hughes Institute, 2665 Long Lake Road, St.  
 Paul, MN 55113, United States  
 SOURCE: Clinical Cancer Research, (1999) 5/6 (1569-1582).  
 Refs: 42  
 ISSN: 1078-0432 CODEN: CCREF4  
 COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article  
 FILE SEGMENT: 016 Cancer  
 025 Hematology  
 037 Drug Literature Index  
 LANGUAGE: English  
 SUMMARY LANGUAGE: English

L1 ANSWER 51 OF 52 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.  
 TI Quantitative high-performance liquid chromatographic method for  
 pharmacokinetic studies of the potent mast cell inhibitor  
 4-(4'-hydroxyphenyl)amino-6,7-dimethoxyquinazoline (WHI-  
 P131).  
 AB The novel quinazoline derivative 4-(4'-hydroxyphenyl)amino-6,7-  
 dimethoxyquinazoline (WHI-P131) has recently been  
 identified as a potent mast cell inhibitor capable of preventing  
 IgE/antigen induced cutaneous as well as systemic fatal anaphylaxis in  
 mice. Here we describe a sensitive high-performance liquid chromatography  
 (HPLC)-based quantitative detection method for measurement of WHI-  
 P131 levels in plasma as well as in target mast cells. The  
 average extraction recovery for WHI-P131 was 88.4% for  
 plasma and 75.7% for RBL-2H3 mast cell lysates. Good linearity ( $r > 0.999$ )  
 was observed throughout the concentration range of 0.1-20  $\mu\text{M}$  in plasma  
 and 0.01-5 nmol in 5.106 cells (0.5-238  $\mu\text{M}$  per cell) for WHI-  
 P131. Intra- and inter-assay variabilities were  $< 7\%$  and the lowest-  
 detection limit of WHI-P131 was 0.05  $\mu\text{M}$  in plasma  
 and 0.005 nmol in 5 million cells, respectively, at a signal-to-noise  
 ratio of  $\text{apprx.} 2$ . The practical utility of this new HPLC method was  
 confirmed in a pilot pharmacokinetic study in BALB/c mice as well as in a  
 cellular drug uptake and disposition study in RBL-2H3 mast cells. After  
 intraperitoneal administration of a non-toxic 40 mg/kg bolus dose of  
 WHI-P131, the estimated maximum plasma concentration was  
 92.7  $\mu\text{M}$ , which is approximately 1-log higher than the effective in  
 vitro mast cell inhibitory concentrations of WHI-P131.  
 The drug absorption was rapid with an absorption half-life of only 2.9 min  
 and the estimated time to reach the maximum plasma concentration was 8.3  
 min. WHI-P131 was cleared with an apparent systemic  
 clearance rate of 2586 ml/h/kg and an elimination half-life of 1.8 h. An  
 intracellular exposure level (AUC) of 55  $\mu\text{M}\cdot\text{h}$  was obtained after in  
 vitro treatment of RBL-2H3 mast cells with WHI-P131 at  
 a 33.6  $\mu\text{M}$  final concentration in culture medium. The availability of  
 the described quantitative HPLC detection method for WHI-  
 P131 provides the basis for further development of WHI-  
 P131 as an anti-allergic drug through detailed pharmacodynamic  
 studies in preclinical animal models. Copyright (C) 1999 Elsevier Science  
 B.V.

ACCESSION NUMBER: 1999143467 EMBASE  
 TITLE: Quantitative high-performance liquid chromatographic method  
 for pharmacokinetic studies of the potent mast cell  
 inhibitor 4-(4'-hydroxyphenyl)amino-6,7-  
 dimethoxyquinazoline (WHI-P131).  
 AUTHOR: Chen C.-L.; Malaviya R.; Chen H.; Liu X.-P.; Uckun F.M.  
 CORPORATE SOURCE: F.M. Uckun, Department Pharmaceutical Sci., Hughes  
 Institute, St. Paul, MN, United States.  
 fatih-uckun@mercury.ih.org  
 SOURCE: Journal of Chromatography B: Biomedical Sciences and

Applications, (1999) 727/1-2 (205-212).

Refs: 15

ISSN: 0378-4347 CODEN: JCBBEP

PUBLISHER IDENT.: S 0378-4347(99)00047-X

COUNTRY: Netherlands

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 026 Immunology, Serology and Transplantation

029 Clinical Biochemistry

030 Pharmacology

037 Drug Literature Index

039 Pharmacy

LANGUAGE: English

SUMMARY LANGUAGE: English

L1 ANSWER 52 OF 52 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.

TI Inhibition of human glioblastoma cell adhesion and invasion by 4-(4'-hydroxylphenyl)-amino-6,7-dimethoxyquinazoline (WHI-P131) and 4-(3'-bromo-4'-hydroxylphenyl)amino-6,7-dimethoxyquinazoline (WHI-P154).

AB Glioblastoma multiforme is a highly invasive primary brain tumor with a disappointingly high local recurrence rate and mortality despite intensive multimodality treatment programs. Therefore, new agents that are capable of inhibiting the infiltration of normal brain parenchyma by glioblastoma cells are urgently needed. Here, we show that the novel quinazoline derivatives 4-(4'-hydroxylphenyl)-amino-6,7-dimethoxyquinazoline (WHI-P131) and 4-(3'-bromo-4'-hydroxylphenyl)-amino-6,7-dimethoxyquinazoline (WHI-P154) are potent inhibitors of glioblastoma cell adhesion and migration. Specifically, both compounds inhibited at micromolar concentrations: (a) integrin-mediated glioblastoma cell adhesion to the extracellular matrix proteins laminin, type IV collagen, and fibronectin; (b) integrin-independent epidermal growth factor-induced adhesion of glioblastoma cells to poly-L-lysine-coated tissue culture plates; (c) fetal bovine serum-induced polymerization of actin and actin stress fiber formation as well epidermal growth factor-stimulated formation of focal adhesion plaques in serum-starved glioblastoma cells; and most importantly, (d) glioblastoma cell migration in in vitro assays of tumor cell invasiveness using tumor cell spheroids and/or Matrigel-coated Boyden chambers. Further preclinical development of WHI-P131 and WHI-P154 may provide the basis for the design of more effective adjuvant chemotherapy programs for glioblastoma multiforme.

ACCESSION NUMBER: 1998352446 EMBASE

TITLE: Inhibition of human glioblastoma cell adhesion and invasion by 4-(4'-hydroxylphenyl)-amino-6,7-dimethoxyquinazoline (WHI-P131) and 4-(3'-bromo-4'-hydroxylphenyl)amino-6,7-dimethoxyquinazoline (WHI-P154).

AUTHOR: Narla R.K.; Liu X.-P.; Klis D.; Uckun F.M.

CORPORATE SOURCE: F.M. Uckun, Wayne Hughes Institute, 2665 Long Lake Road, St. Paul, MN 55113, United States

SOURCE: Clinical Cancer Research, (1998) 4/10 (2463-2471).

Refs: 45

ISSN: 1078-0432 CODEN: CCREF4

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 008 Neurology and Neurosurgery

016 Cancer

037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

=> d his

(FILE 'HOME' ENTERED AT 13:19:41 ON 08 MAY 2003)

FILE 'WPIDS, MEDLINE, BIOSIS, DGENE, EMBASE, JAPIO, FSTA, JICST-EPLUS'  
ENTERED AT 13:21:46 ON 08 MAY 2003

L1 52 S WHI-P131  
L2 11 S JAK-3 INHIBITORS  
L3 73225 S GRAFT VERSUS HOST DISEASE

=> d l2 ti abs ibib tot

L2 ANSWER 1 OF 11 WPIDS (C) 2003 THOMSON DERWENT  
TI New Janus Kinase-3 inhibitors for treating allergic disorders.  
AN 2002-065579 [09] WPIDS  
CR 2000-451222 [39]; 2000-451223 [39]; 2001-201837 [20]; 2002-088962 [12];  
2002-443753 [47]; 2003-174595 [17]  
AB US 6313130 B UPAB: 20030312  
NOVELTY - Janus Kinase-3 (JAK-3) inhibitors  
are new. The inhibitors have a molecular dimension compatible with the  
shape of a JAK-3 kinase binding pocket model occupying a molecular volume  
of 200 - 400 (preferably 225 - 350) Angstrom 3.  
ACTIVITY - Antiallergic; Immunosuppressive; Antiinflammatory;  
Antiasthmatic; Dermatological.  
MECHANISM OF ACTION - Mast cell activation or degranulation  
inhibitor. RBL-2H3 mast cells were preincubated with 4-(6,7-dimethoxy-  
quinazolin-4-ylamino)-phenol and 2-bromo-4-(6,7-dimethoxy-quinazolin-4-  
ylamino)-phenol (test compounds)/3-bromo-4-methyl-phenyl)-(6,7-dimethoxy-  
quinazolin-4-yl)-amine and 2,5-dibromo-phenyl)-(6,7-dimethoxy-quinazolin-4-  
yl)-amine (control compounds) for 1 hour before challenge with antigen  
(DNP-BSA). Stimulation of RBL-2H3 mast cells using IgE/antigen resulted in  
release of beta -hexosaminidase and TNFa. The test compounds showed an  
inhibition of at least 30 mu M. The results obtained showed that the test  
compounds prevented mast cell degranulation and release of preformed  
granule-associated beta -hexosaminidase as well as the newly synthesized  
arachidonic acid metabolite and the proinflammatory cytokine TNFa, while  
the comparative compounds did not inhibit mast cell granulation or  
mediator release after IgE receptor/Fc epsilon RI crosslinking.  
USE - For treating pathologies such as immediate hypersensitivity  
reaction, anaphylaxis, allergic rhinitis, allergic urticaria, angioedema,  
allergic asthma and allergic reaction to insect bites, food, drugs and  
pollen, in mammals e.g. humans (claimed).  
ADVANTAGE - The inhibitors implicate and inhibit mast cell activation  
or degranulation. The inhibitors play a pivotal role in IgE receptor/Fc  
epsilon RI mediated mast cell responses both in vitro and in vivo. The  
JAK-3 inhibition therefore results in reduced or inhibited degranulation  
and proinflammatory mediator release.

Dwg.0/15

ACCESSION NUMBER: 2002-065579 [09] WPIDS  
CROSS REFERENCE: 2000-451222 [39]; 2000-451223 [39]; 2001-201837 [20];  
2002-088962 [12]; 2002-443753 [47]; 2003-174595 [17]  
DOC. NO. CPI: C2002-019363  
TITLE: New Janus Kinase-3 inhibitors for treating allergic  
disorders.  
DERWENT CLASS: B02  
INVENTOR(S): MALAVIYA, R; SUDBECK, E A; UCKUN, F M  
PATENT ASSIGNEE(S): (PARK-N) PARKER HUGHES INST  
COUNTRY COUNT: 1  
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 6313130	B1	20011106	(200209)*		48

APPLICATION DETAILS:



PATENT NO	KIND	APPLICATION	DATE
US 6313130	B1 Cont of	US 1999-263420	19990305
	Cont of	US 1999-443847	19991119
		US 2000-627342	20000728

FILING DETAILS:

PATENT NO	KIND	PATENT NO
US 6313130	B1 Cont of	US 6080747
	Cont of	US 6177433

PRIORITY APPLN. INFO: US 1999-263420 19990305; US 1999-443847  
19991119; US 2000-627342 20000728

L2 ANSWER 2 OF 11 WPIDS (C) 2003 THOMSON DERWENT  
 TI New quinazoline derivatives useful for treating leukemia, lymphoma and skin cancer.  
 AN 2000-224646 [19] WPIDS  
 AB WO 200010981 A UPAB: 20021105  
 NOVELTY - Novel 4-phenyl-(amino, thio, oxy, or methyl)-quinazoline derivatives are claimed which are inhibitors of JAK-3 (a member of the Janus family of tyrosine kinases).  
 DETAILED DESCRIPTION - A pharmaceutical composition comprises quinazoline derivatives of formula (I) or their salts and a carrier.  
 X = HN, NR11, S, O, CH2 or R11CH;  
 R11 = H, 1-4C alkyl or 1-4C alkanoyl;  
 R1-R8 = H, OH, SH, NH2, NO2, 1-4C alkyl, 1-4C alkoxy, 1-4C alkylthio or halo; or  
 2 adjacent R1-R5+phenyl ring = a fused ring e.g. naphthyl or tetrahydro-naphthyl, optionally substituted by 1-4 OH, SH, NH2, NO2, 1-4C alkyl, 1-4C alkoxy, 1-4C alkylthio, or halo;  
 R9, R10 = H, 1-4C alkyl, 1-4C alkoxy, halo, or 1-4C alkanoyl; or  
 R9 + R10 = methylenedioxy.  
 An INDEPENDENT CLAIM is included for novel compounds (I) provided that the compound is not 4-(4'-hydroxyphenyl)amino-6,7-dimethoxy-quinazoline.  
 ACTIVITY - Cytostatic; Immunosuppressive; Antiinflammatory; Immunostimulant.  
 JAK3-deficient males and their WT littermates, rendered diabetic by STZ, were transplanted with BALB/c islets under the kidney capsule and blood glucose level was followed for 100 days post transplantation while islet allografts of WT controls were rejected with a MST of 12.9 days, all islet allografts of JAK3 recipients survived 100 days past transplantation.  
 MECHANISM OF ACTION - Janus tyrosine kinase-3 (JAK-) Inhibitor  
 USE - (I) are **JAK-3 inhibitors** useful for treating leukemia, lymphoma, organ transplant rejection; for preventing or reducing UVB radiation-induced inflammatory response, UVB-induced skin edema or vascular permeability changes or UVB radiation-induced damage to epithelial cells or mutation frequency in skin; for inhibiting the release of prostaglandin E2; for protecting a mammal from tumorigenic effects of UVB light; for inhibiting T-cell activity; for treating autoimmune disease and for preventing or treating graft-versus-host disease after bone marrow transplantation (claimed). The compounds may be used for treating diabetes and asthma.  
 Dwg.0/42  
 ACCESSION NUMBER: 2000-224646 [19] WPIDS  
 DOC. NO. CPI: C2000-068707  
 TITLE: New quinazoline derivatives useful for treating leukemia, lymphoma and skin cancer.  
 DERWENT CLASS: B02  
 INVENTOR(S): CETKOVIC, M; LIU, X; MALAVIYA, R; UCKUN, F M; SUDBECK, E

A; MAHAJAN, S; NAVARA, C S  
 PATENT ASSIGNEE(S): (HUGH-N) HUGHES INST; (PARK-N) PARKER HUGHES INST  
 COUNTRY COUNT: 89  
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000010981	A1	20000302	(200019)	* EN	130
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW					
AU 9956827	A	20000314	(200031)		
NO 2001000887	A	20010423	(200130)		
EP 1105378	A1	20010613	(200134)	EN	
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					
US 6313129	B1	20011106	(200170)		
US 2001044442	A1	20011122	(200176)		
KR 2001089171	A	20010929	(200220)		
US 2002042513	A1	20020411	(200227)		
HU 2001003386	A2	20020429	(200238)		
JP 2002523403	W	20020730	(200264)		160
US 6469013	B2	20021022	(200273)		
US 6495556	B2	20021217	(200307)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000010981	A1	WO 1999-US19043	19990820
AU 9956827	A	AU 1999-56827	19990820
NO 2001000887	A	WO 1999-US19043	19990820
		NO 2001-887	20010221
EP 1105378	A1	EP 1999-943800	19990820
		WO 1999-US19043	19990820
US 6313129	B1 Provisional	US 1998-97359P	19980821
	Provisional	US 1998-97365P	19980821
		US 1999-378093	19990820
US 2001044442	A1 Provisional	US 1998-97359P	19980821
	Provisional	US 1998-97365P	19980821
	Cont of	US 1999-378093	19990820
		US 2001-812098	20010319
KR 2001089171	A	KR 2001-702230	20010221
US 2002042513	A1 Provisional	US 1998-97359P	19980821
	Provisional	US 1998-97365P	19980821
	Div ex	US 1999-378093	19990820
	Div ex	US 2000-688756	20001016
		US 2001-858824	20010516
HU 2001003386	A2	WO 1999-US19043	19990820
		HU 2001-3386	19990820
JP 2002523403	W	WO 1999-US19043	19990820
		JP 2000-566255	19990820
US 6469013	B2 Provisional	US 1998-97359P	19980821
	Provisional	US 1998-97365P	19980821
	Div ex	US 1999-378093	19990820
	Div ex	US 2000-688756	20001016
		US 2001-858824	20010516
US 6495556	B2 Provisional	US 1998-97359P	19980821
	Provisional	US 1998-97365P	19980821
	Cont of	US 1999-378093	19990820
		US 2001-812098	20010319

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 9956827	A Based on	WO 200010981
EP 1105378	A1 Based on	WO 200010981
US 2002042513	A1 Div ex	US 6313129
HU 2001003386	A2 Based on	WO 200010981
JP 2002523403	W Based on	WO 200010981
US 6469013	B2 Div ex	US 6313129

PRIORITY APPLN. INFO: US 1998-97365P 19980821; US 1998-97359P  
 19980821; US 1999-378093 19990820; US  
 2001-812098 20010319; US 2000-688756  
 20001016; US 2001-858824 20010516

L2 ANSWER 3 OF 11 WPIDS (C) 2003 THOMSON DERWENT  
 TI New quinazoline Janus family kinase 3 inhibitors, used for treating, e.g.  
 pathological conditions in mammalian or avian cells.  
 AN 2000-170884 [15] WPIDS  
 AB WO 200000202 A UPAB: 20000323

NOVELTY - Quinazolines and their salts are new.  
 DETAILED DESCRIPTION - Quinazolines are of formula (I):  
 X = HN, R11N, S, O, CH2 or R11CH;  
 R11 = H, 1-4C alkyl or 1-4C alkanoyl;  
 R1-R8 = H, OH, mercapto, amino, nitro, 1-4C alkyl, 1-4C alkoxy, 1-4C  
 alkylthio, halo or, two adjacent of R1-R5, together with the phenyl ring  
 to which they are attached, form naphthyl or tetrahydronaphthyl optionally  
 substituted by 1-4 of hydroxy, mercapto, amino, nitro, 1-4C alkyl, 1-4C  
 alkoxy, 1-4C alkylthio or halo; and  
 R9, R10 = H, 1-4C alkyl, 1-4C alkoxy, halo or 1-4C alkanoyl, or,  
 together, form methylenedioxy.

An INDEPENDENT CLAIM is also included for (1) method comprising  
 inhibiting c-jun activation in mammalian or avian cells by contacting  
 cells with substance that inhibits activity of Janus family kinase 3  
 (JAK-3).

ACTIVITY - Cytoprotective.

MECHANISM OF ACTION - JAK-3 inhibitor; c-jun activation inhibitor.  
 DT-40 cells were treated with 4-(3'-bromo-4'-hydroxyphenyl)-amino-6,7-  
 dimethoxyquinazoline (Ia) (100 mg/ml) for 24 hours at 37 deg. C prior to  
 exposure to 20 Gy ionizing radiation. Ionizing radiation failed to induce  
 c-jun expression in the DT-40 cells demonstrating that **JAK-3 inhibitors**  
 are capable of inhibiting radiation induced c-jun expression.

USE - Used to prevent or treat pathological conditions in mammalian  
 or avian cells where c-jun activation is implicated such as from exposure  
 of cells to radiation or to chemical agents that cause DNA damage e.g.  
 ara-C, topoisomerase II inhibitors, UV radiation, alkylating agents or  
 ionizing radiation, including tissue damage, organ (heart, liver, kidney)  
 damage, inflammation, hair loss or negative effects produced by oxygen  
 free radicals during chemotherapy (claimed). Also used to treat conditions  
 resulting from action of internally generated oxygen free radicals such as  
 aging and amyelotrophic lateral sclerosis.

ADVANTAGE - Selective **JAK-3 inhibitors**  
 do not inhibit JAK-1 or JAK-2. Effects of test compounds on enzymatic  
 activity of JAK-1, JAK-2 and JAK-3 was examined in Sf21 cells infected  
 with baculovirus expression vectors for the kinases. Kinase assays were  
 performed 1 hour following 1-hour exposure of immunoprecipitated JAKs to  
 test compounds. Results showed that the two compounds tested (Ia) and  
 4-(3'-bromo-4'-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline inhibited  
 JAK-3, but not JAK-1 or JAK-2.

Dwg.0/5

ACCESSION NUMBER: 2000-170884 [15] WPIDS  
 DOC. NO. CPI: C2000-053053

TITLE: New quinazoline Janus family kinase 3 inhibitors, used for treating, e.g. pathological conditions in mammalian or avian cells.

DERWENT CLASS: B02 B04 C02 C03

INVENTOR(S): UCKUN, F M

PATENT ASSIGNEE(S): (HUGH-N) HUGHES INST; (UCKU-I) UCKUN F M; (PARK-N) PARKER HUGHES INST

COUNTRY COUNT: 87

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000000202	A1	20000106	(200015)*	EN	49
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW					
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW					
AU 9948515	A	20000117	(200026)		
EP 1091739	A1	20010418	(200123)	EN	
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000000202	A1	WO 1999-US14923	19990630
AU 9948515	A	AU 1999-48515	19990630
EP 1091739	A1	EP 1999-932145	19990630
		WO 1999-US14923	19990630

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 9948515	A Based on	WO 200000202
EP 1091739	A1 Based on	WO 200000202

PRIORITY APPLN. INFO: US 1998-91150P 19980630

L2 ANSWER 4 OF 11 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

TI Dimethoxy quinazolines for treating diabetes.

AB The invention provides novel **JAK-3 inhibitors** that are useful for treating leukemia and lymphoma. The compounds are also useful to treat or prevent skin cancer, as well as sunburn and UVB-induced skin inflammation. In addition, the compounds of the present invention prevent the immunosuppressive effects of UVB radiation, and are useful to treat or prevent autoimmune diseases, inflammation, and transplant rejection. The invention also provides pharmaceutical compositions comprising compounds of the invention, as well as therapeutic methods for their use.

ACCESSION NUMBER: 2003:71032 BIOSIS

DOCUMENT NUMBER: PREV200300071032

TITLE: Dimethoxy quinazolines for treating diabetes.

AUTHOR(S): Uckun, Fatih M. (1); Sudbeck, Elise A.; Cetkovic, Marina; Malaviya, Ravi; Liu, Xing-Ping

CORPORATE SOURCE: (1) White Bear Lake, MN, USA USA  
ASSIGNEE: Parker Hughes Institute

PATENT INFORMATION: US 6495556 December 17, 2002

SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Dec. 17 2002) Vol. 1265, No. 3, pp. No  
Pageination. <http://www.uspto.gov/web/menu/patdata.html>.  
e-file.

ISSN: 0098-1133.

DOCUMENT TYPE: Patent  
LANGUAGE: English

L2 ANSWER 5 OF 11 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

TI **JAK-3 inhibitors** for treating allergic disorders.

AB Inhibitors of JAK3 kinase for the treatment of allergy inhibit mast cell degranulation and mediator release.

ACCESSION NUMBER: 2002:583136 BIOSIS

DOCUMENT NUMBER: PREV200200583136

TITLE: **JAK-3 inhibitors** for treating allergic disorders.

AUTHOR(S): Uckun, Fatih M.; Malaviya, Ravi; Sudbeck, Elise A.

ASSIGNEE: Parker Hughes Institute

PATENT INFORMATION: US 6452005 September 17, 2002

SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Sep. 17, 2002) Vol. 1262, No. 3, pp. No  
Pagination. <http://www.uspto.gov/web/menu/patdata.html>.  
e-file.

ISSN: 0098-1133.

DOCUMENT TYPE: Patent  
LANGUAGE: English

L2 ANSWER 6 OF 11 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

TI **JAK-3 inhibitors** for treating allergic disorders.

AB Inhibitors of JAK3 kinase for the treatment of allergy inhibit mast cell degranulation and mediator release.

ACCESSION NUMBER: 2002:74128 BIOSIS

DOCUMENT NUMBER: PREV200200074128

TITLE: **JAK-3 inhibitors** for treating allergic disorders.

AUTHOR(S): Uckun, Fatih M.; Malaviya, Ravi; Sudbeck, Elise A.

ASSIGNEE: Parker Hughes Institute

PATENT INFORMATION: US 6326373 December 04, 2001

SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Dec. 4, 2001) Vol. 1253, No. 1, pp. No  
Pagination. <ftp://ftp.uspto.gov/pub/patdata/>. e-file.

ISSN: 0098-1133.

DOCUMENT TYPE: Patent  
LANGUAGE: English

L2 ANSWER 7 OF 11 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

TI **JAK-3 inhibitors** for treating allergic disorders.

AB Inhibitors of JAK3 kinase for the treatment of allergy inhibit mast cell degranulation and mediator release.

ACCESSION NUMBER: 2002:39602 BIOSIS

DOCUMENT NUMBER: PREV200200039602

TITLE: **JAK-3 inhibitors** for treating allergic disorders.

AUTHOR(S): Uckun, Fatih M.; Malaviya, Ravi; Sudbeck, Elise A.

ASSIGNEE: Parker Hughes Institute

PATENT INFORMATION: US 6313130 November 06, 2001

SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Nov. 6, 2001) Vol. 1252, No. 1, pp. No  
Pagination. e-file.

ISSN: 0098-1133.

DOCUMENT TYPE: Patent  
LANGUAGE: English

L2 ANSWER 8 OF 11 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

TI Therapeutic compounds.

AB The invention provides novel **JAK-3 inhibitors** that are useful for treating leukemia and lymphoma. The compounds are also useful to treat or prevent skin cancer, as well as sunburn and UVB-induced skin inflammation. In addition, the compounds of the present invention prevent the immunosuppressive effects of UVB radiation, and are useful to treat or prevent autoimmune diseases, inflammation, and transplant rejection. The invention also provides pharmaceutical compositions comprising compounds of the invention, as well as therapeutic methods for their use.

ACCESSION NUMBER: 2002:7690 BIOSIS  
DOCUMENT NUMBER: PREV200200007690  
TITLE: Therapeutic compounds.  
AUTHOR(S): Uckun, Fatih M.; Sudbeck, Elise A.; Cetkovic, Marina (1);  
Malaviya, Ravi; Liu, Xing-Ping  
CORPORATE SOURCE: (1) Maplewood, MN USA  
ASSIGNEE: Hughes Institute, St, Paul, MN, USA  
PATENT INFORMATION: US 6313129 November 06, 2001  
SOURCE: Official Gazette of the United States Patent and Trademark  
Office Patents, (Nov. 6, 2001) Vol. 1252, No. 1, pp. No  
Pagination. e-file.  
ISSN: 0098-1133.  
DOCUMENT TYPE: Patent  
LANGUAGE: English

L2 ANSWER 9 OF 11 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

TI **JAK-3 inhibitors** for treating allergic disorders.

AB Inhibitors of JAK3 kinase for the treatment of allergy inhibit mast cell degranulation and mediator release.

ACCESSION NUMBER: 2001:350387 BIOSIS  
DOCUMENT NUMBER: PREV200100350387  
TITLE: **JAK-3 inhibitors** for treating  
allergic disorders.  
AUTHOR(S): Uckun, Fatih M.; Malaviya, Ravi; Sudbeck, Elise A.  
ASSIGNEE: Parker Hughes Institute  
PATENT INFORMATION: US 6177433 January 23, 2001  
SOURCE: Official Gazette of the United States Patent and Trademark  
Office Patents, (Jan. 23, 2001) Vol. 1242, No. 4, pp. No  
Pagination. e-file.  
ISSN: 0098-1133.  
DOCUMENT TYPE: Patent  
LANGUAGE: English

L2 ANSWER 10 OF 11 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

TI Therapeutic use of **JAK-3 inhibitors**.

AB Inhibitors of JAK3 kinase for the treatment of allergy inhibit mast cell degranulation and mediator release.

ACCESSION NUMBER: 2001:122095 BIOSIS  
DOCUMENT NUMBER: PREV200100122095  
TITLE: Therapeutic use of **JAK-3 inhibitors**.  
AUTHOR(S): Uckun, Fatih M.; Malaviya, Ravi; Sudbeck, Elise A.  
ASSIGNEE: Parker Hughes Institute, Roseville, MN, USA  
PATENT INFORMATION: US 6080748 June 27, 2000  
SOURCE: Official Gazette of the United States Patent and Trademark  
Office Patents, (June 27, 2000) Vol. 1235, No. 4, pp. No  
Pagination. e-file.  
ISSN: 0098-1133.  
DOCUMENT TYPE: Patent  
LANGUAGE: English

L2 ANSWER 11 OF 11 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

TI **JAK-3 inhibitors** for treating allergic disorders.

AB Inhibitors of JAK3 kinase for the treatment of allergy inhibit mast cell degranulation an dmediator release.  
ACCESSION NUMBER: 2001:122094 BIOSIS  
DOCUMENT NUMBER: PREV200100122094  
TITLE: **JAK-3 inhibitors** for treating allergic disorders.  
AUTHOR(S): Uckun, Fatih M.; Malavia, Ravi (1); Sudbeck, Elise A.  
CORPORATE SOURCE: (1) Shoreview, MN USA  
ASSIGNEE: Hughes Institute  
PATENT INFORMATION: US 6080747 June 27, 2000  
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (June 27, 2000) Vol. 1235, No. 4, pp. No  
Pagination. e-file.  
ISSN: 0098-1133.  
DOCUMENT TYPE: Patent  
LANGUAGE: English

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(FILE 'HOME' ENTERED AT 13:19:41 ON 08 MAY 2003)

FILE 'WPIDS, MEDLINE, BIOSIS, DGENE, EMBASE, JAPIO, FSTA, JICST-EPLUS'  
ENTERED AT 13:21:46 ON 08 MAY 2003

L1 52 S WHI-P131  
L2 11 S JAK-3 INHIBITORS  
L3 73225 S GRAFT VERSUS HOST DISEASE

=> s l3 and jak-3

L4 1 L3 AND JAK-3

=> d l4 ti abs ibib

L4 ANSWER 1 OF 1 WPIDS (C) 2003 THOMSON DERWENT  
TI New quinazoline derivatives useful for treating leukemia, lymphoma and skin cancer.  
AN 2000-224646 [19] WPIDS  
AB WO 200010981 A UPAB: 20021105  
NOVELTY - Novel 4-phenyl-(amino, thio, oxy, or methyl)-quinazoline derivatives are claimed which are inhibitors of **JAK-3** (a member of the Janus family of tyrosine kinases).  
DETAILED DESCRIPTION - A pharmaceutical composition comprises quinazoline derivatives of formula (I) or their salts and a carrier.  
X = HN, NR11, S, O, CH2 or R11CH;  
R11 = H, 1-4C alkyl or 1-4C alkanoyl;  
R1-R8 = H, OH, SH, NH2, NO2, 1-4C alkyl, 1-4C alkoxy, 1-4C alkylthio or halo; or  
2 adjacent R1-R5+phenyl ring = a fused ring e.g. naphthyl or tetrahydro-naphthyl, optionally substituted by 1-4 OH, SH, NH2, NO2, 1-4C alkyl, 1-4C alkoxy, 1-4C alkylthio, or halo;  
R9, R10 = H, 1-4C alkyl, 1-4C alkoxy, halo, or 1-4C alkanoyl; or  
R9 + R10 = methylenedioxy.  
An INDEPENDENT CLAIM is included for novel compounds (I) provided that the compound is not 4-(4'-hydroxyphenyl)amino-6,7-dimethoxy-quinazoline.  
ACTIVITY - Cytostatic; Immunosuppressive; Antiinflammatory; Immunostimulant.  
JAK3-deficient males and their WT littermates, rendered diabetic by STZ, were transplanted with BALB/c islets under the kidney capsule and blood glucose level was followed for 100 days post transplantation while islet allografts of WT controls were rejected with a MST of 12.9 days, all islet allografts of JAK3 recipients survived 100 days past transplantation.  
MECHANISM OF ACTION - Janus tyrosine kinase-3 (JAK-) Inhibitor

USE - (I) are JAK-3 inhibitors useful for treating leukemia, lymphoma, organ transplant rejection; for preventing or reducing UVB radiation-induced inflammatory response, UVB-induced skin edema or vascular permeability changes or UVB radiation-induced damage to epithelial cells or mutation frequency in skin; for inhibiting the release of prostaglandin E2; for protecting a mammal from tumorigenic effects of UVB light; for inhibiting T-cell activity; for treating autoimmune disease and for preventing or treating graft-versus-host disease after bone marrow transplantation (claimed). The compounds may be used for treating diabetes and asthma.

Dwg.0/42

ACCESSION NUMBER: 2000-224646 [19] WPIDS  
 DOC. NO. CPI: C2000-068707  
 TITLE: New quinazoline derivatives useful for treating leukemia, lymphoma and skin cancer.  
 DERWENT CLASS: B02  
 INVENTOR(S): CETKOVIC, M; LIU, X; MALAVIYA, R; UCKUN, F M; SUDBECK, E A; MAHAJAN, S; NAVARA, C S  
 PATENT ASSIGNEE(S): (HUGH-N) HUGHES INST; (PARK-N) PARKER HUGHES INST  
 COUNTRY COUNT: 89  
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000010981	A1	20000302	(200019)*	EN	130
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW					
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW					
AU 9956827	A	20000314	(200031)		
NO 2001000887	A	20010423	(200130)		
EP 1105378	A1	20010613	(200134)	EN	
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					
US 6313129	B1	20011106	(200170)		
US 2001044442	A1	20011122	(200176)		
KR 2001089171	A	20010929	(200220)		
US 2002042513	A1	20020411	(200227)		
HU 2001003386	A2	20020429	(200238)		
JP 2002523403	W	20020730	(200264)		160
US 6469013	B2	20021022	(200273)		
US 6495556	B2	20021217	(200307)		

# APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000010981	A1	WO 1999-US19043	19990820
AU 9956827	A	AU 1999-56827	19990820
NO 2001000887	A	WO 1999-US19043	19990820
		NO 2001-887	20010221
EP 1105378	A1	EP 1999-943800	19990820
		WO 1999-US19043	19990820
US 6313129	B1 Provisional	US 1998-97359P	19980821
	Provisional	US 1998-97365P	19980821
		US 1999-378093	19990820
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US 2002042513	A1 Provisional	US 1998-97359P	19980821
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	Div ex	US 2000-688756	20001016
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HU 2001003386	A2	WO 1999-US19043	19990820
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HU 2001003386	A2 Based on	WO 200010981
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